

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing (day/month/year)</b> 23 March 1998 (23.03.98)	<b>Applicant's or agent's file reference</b> PHM 70185/WO
<b>International application No.</b> PCT/GB97/02212	<b>Priority date (day/month/year)</b> 17 August 1996 (17.08.96)
<b>International filing date (day/month/year)</b> 13 August 1997 (13.08.97)	
<b>Applicant</b> BOYLE, Francis, Thomas et al	

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

16 February 1998 (16.02.98)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland	<b>Authorized officer</b> F. Gateau
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38



## TENT COOPERATION TRE

09 214461

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

To:

DRURY, Peter, Lawrence  
T&N Limited  
Manchester International Office  
Centre  
Styal Road  
Manchester M22 5TN  
ROYAUME-UNI

Date of mailing (day/month/year) 08 January 1999 (08.01.99)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference TNT 2531	
International application No. PCT/GB97/01827	International filing date (day/month/year) 04 July 1997 (04.07.97)

## 1. The following indications appeared on record concerning:

☐ the applicant
 ☐ the inventor
 ☒ the agent
 ☐ the common representative

## Name and Address

DRURY, Peter, Lawrence  
T & N plc  
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United Kingdom

## State of Nationality

## State of Residence

## Telephone No.

0161 872 0155

## Facsimile No.

0161 848 0354

## Teleprinter No.

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person
 ☐ the name
 ☒ the address
 ☐ the nationality
 ☐ the residence

## Name and Address

DRURY, Peter, Lawrence  
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Manchester International Office  
Centre  
Styal Road  
Manchester M22 5TN  
United Kingdom

## State of Nationality

## State of Residence

## Telephone No.

0161 955 5270

## Facsimile No.

0161 955 5241

## Teleprinter No.

## 3. Further observations, if necessary:

## 4. A copy of this notification has been sent to:

☒ the receiving Office
 ☐ the designated Offices concerned  
☐ the International Searching Authority
 ☒ the elected Offices concerned  
☐ the International Preliminary Examining Authority
 ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  Ting Zhao  Telephone No.: (41-22) 338.83.38
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# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

19  
REC'D 10 DEC 1998

Applicant's or agent's file reference <b>PHM 70185/WO</b>	<b>FOR FURTHER ACTION</b>		See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
International application No. <b>PCT/GB97/02212</b>	International filing date (day/month/year) <b>13/08/1997</b>	Priority date (day/month/year) <b>17/08/1996</b>	
International Patent Classification (IPC) or national classification and IPC <b>C07D207/12</b>			
Applicant <b>ZENECA LIMITED et al.</b>			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
  - ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  <b>16/02/1998</b>	Date of completion of this report  <b>07.12.98</b>
Name and mailing address of the IPEA/  <div style="display: flex; align-items: center;"> <div> <b>European Patent Office</b>  <b>D-80298 Munich</b>                      Tel. (+49-89) 2399-0, Tx: 523656 epmu d                      Fax: (+49-89) 2399-4465                 </div> </div>	Authorized officer  <b>Herz, C</b>  Telephone No. (+49-89) 2399-8275  <div style="text-align: right;"> </div>



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB97/02212

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-63,65-77 as originally filed

64 as received on 09/10/1998 with letter of 06/10/1998

**Claims, No.:**

1-13 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.  
☒ claims Nos. 10.

because:

- ☒ the said international application, or the said claims Nos. 10 relate to the following subject matter which does not require an international preliminary examination (*specify*):



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB97/02212

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

**2. Citations and explanations**

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/GB97/02212

1. Claim 10 is directed to a therapeutical method performed on humans. Under the terms of Rule 67.1 (iv) PCT, the International Preliminary Examination Authority is not required to carry out an examination on such claim.

2. Prior art as represented by document EP-A-0 696 593 (A) cited in the International Search Report discloses proline amides exhibiting farnesyl transferase inhibitory action. Thus, the technical problem underlying the present application was to provide other pyrrolidine compounds showing this activity at an increased level.

Whether this problem has been solved by the provision of the 3-sulfanylpyrrolidines claimed in the present application cannot be inferred from the information available there from. Although there is a statement to be found on page 42 of the application that the compounds claimed possess an  $IC_{50}$  in the range of 0,001 to 200  $\mu$ M, there is no evidence for any superior activity vis-à-vis the closest prior art.

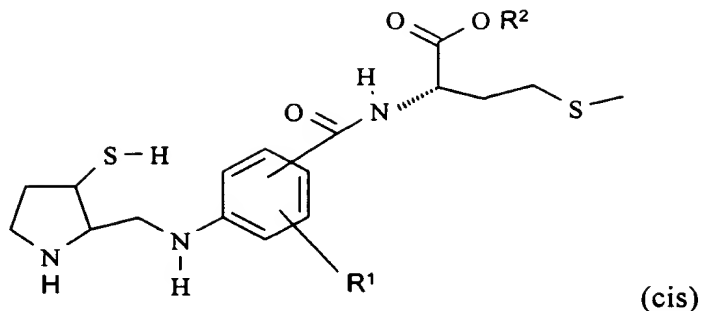
The subject-matter in the present application basically differs from the subject-matter disclosed in the nearest prior art (A) by virtue of the position of the sulfanyl substituent on the pyrrolidine moiety. Variations of the position of certain substituents while the structure of the remaining part of the molecule is not modified are routinely performed when the enhancement of the activity of a given pharmacophore is aimed at. The examples given in the present application thus only represent minor structural modifications of the basic structure.

Taking account these facts the man skilled in the art would have to expect the qualitative retention of the desired activity without affecting their basic capabilities when changing the position of the sulfanyl substituent of the basic structural unit of the compounds disclosed in the state of the art from 4 to 3. Thus representing only predictable effects the compounds claimed are considered to be obvious under Article 33 (3) PCT.

3. The use of the term "side chain of a lipophilic amino acid" throughout the claims without further definitive qualification therein renders these claims obscure in scope in that it does not indicate any specific substituents. As chemical species can be precisely defined by the identity and number of atoms involved (cf. the definitions given on pages 8 to 9) the above terms are considered to render these claims obscure in scope in that it does not indicate any specific substituents. Therefore it is not clear whether the compounds implied fall within the scope of the claims of the present application and/or constitute a solution to the problem underlying the application; the incorporation of the specific substituents given in the specification is therefore necessary (Articles 6, 33 (3) PCT).





Example 12

Compound	R¹	Position of R¹ on phenyl	R²	Position of R² containing substituent on phenyl
47	Ph-	4	Me	3
48	PhCH₂-	4	Me	3
49	PhCH₂CH₂-	4	Me	3
50	4-F-PhCH₂CH₂	3	Me	4
51	PhCH₂CH₂-	4	H	3
52	4-F-PhCH₂CH₂-	3	H	4

5

Compounds 51 and 52 were prepared from compounds 49 and 50 respectively using a similar method to that used to prepare compound 27 (Example 6). Compounds 47, 48, 49 and 50 were prepared by deprotecting the appropriate tritylsulfanyl compounds (compounds 43, 44, 45 and 46 respectively) using a similar method to that of Example 1, step 1.

## 10 Compound 47:

NMR (DMSO-d<sub>6</sub>)  $\delta$ : 1.72-1.88(m, 3H), 1.97(s, 3H), 1.97-2.35(m, 3H), 3.13-3.57(m, 5H), 3.60(s, 3H), 3.65-3.86(m, 2H), 4.30-4.40(m, 1H), 6.70(d, 1H), 6.80(dd, 1H), 7.15-7.32(m, 6H), 8.47-8.53(m, 1H), 9.43(br.s, 1H), 9.90(br.s, 1H).

Micro Analysis:

%Theory C51.70, H6.18, N7.54, S11.50

15 (2.00HCl, 0.60 H<sub>2</sub>O)

%Found C51.90, H6.10, N7.80, S11.60

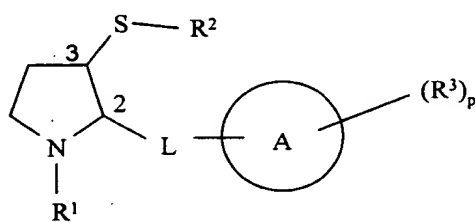


ABSTRACT

5

CHEMICAL COMPOUNDS

The present invention relates to inhibitors of ras farnesylation of the Formula I



Formula I

10 wherein:

R¹ is for example H and further values as defined in the specification; R² is for example H and further values as defined in the specification; R³ is for example H or a substituent having values as defined in the specification; p is 0-3 in which R³ values can be the same or different; L is a linking moiety for example -CH₂NH- and further values as defined in the specification;

15 A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms where the heteroatoms are independently selected from O, N & S; or a -S-S- dimer thereof when R²=H; or a N-oxide or a pharmaceutically-acceptable salt, prodrug or solvate thereof. Processes for their preparation their use as therapeutic agents and pharmaceutical compositions containing them. A particular use is in cancer therapy.

20



INTERNATIONAL COOPERATION TREATY  
**PCT**

**INTERNATIONAL SEARCH REPORT**

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>PHM 70185/WO</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/GB 97/ 02212</b>	International filing date (day/month/year) <b>13/08/1997</b>	(Earliest) Priority Date (day/month/year) <b>17/08/1996</b>
Applicant <b>ZENECA LIMITED et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).
2. ☐ Unity of invention is lacking (see Box II).
3. ☐ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
- ☐ filed with the international application.
  - ☐ furnished by the applicant separately from the international application,
    - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
  - ☐ Transcribed by this Authority

4. With regard to the title, ☐ the text is approved as submitted by the applicant.  
☒ the text has been established by this Authority to read as follows:

**3-Mercaptopyrrolidines as farnesyl protein transferase inhibitors**

5. With regard to the abstract,
- ☒ the text is approved as submitted by the applicant.
  - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. \_\_\_\_\_ ☐ as suggested by the applicant.  
☐ because the applicant failed to suggest a figure.  
☐ because this figure better characterizes the invention.

☒ None of the figures.



# INTERNATIONAL SEARCH REPORT

National Application No

PCT/GB 97/02212

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D207/12 C07D401/12 C07D417/12 C07D403/12 A61K31/40  
A61K31/425 A61K31/44 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 696 593 A (BRISTOL-MYERS SQUIBB CO.) 14 February 1996 cited in the application see claims 1-19 ---	1-13
P,Y	WO 97 06138 A (ZENECA LIMITED) 20 February 1997 see claim 1 ---	1-13
A	WO 96 09821 A (MERCK & CO., INC.) 4 April 1996 see claims 1-24 ---	1-13
A	WO 95 25086 A (EISAI CO., LTD.) 21 September 1995 cited in the application see claims 1-15 -----	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\* & \* document member of the same patent family

Date of the actual completion of the international search

12 November 1997

Date of mailing of the international search report

26. 11. 97

Name and mailing address of the ISA

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Authorized officer

Herz, C





# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 97/02212

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 696593 A	14-02-96	AU 2845395 A CA 2155448 A JP 8059610 A	22-02-96 12-02-96 05-03-96
WO 9706138 A	20-02-97	AU 6622396 A	05-03-97
WO 9609821 A	04-04-96	US 5571835 A AU 3685795 A EP 0783305 A	05-11-96 19-04-96 16-07-97
WO 9525086 A	21-09-95	AU 2122795 A CA 2185441 A EP 0750609 A FI 963597 A NO 963860 A	03-10-95 21-09-95 02-01-97 14-11-96 13-11-96





## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification<sup>6</sup> :C07D 207/12, 401/12, 417/12, 403/12,  
A61K 31/40, 31/425, 31/44, 31/495

A1

(11) International Publication Number:

WO 98/07692

(43) International Publication Date:

26 February 1998 (26.02.98)

(21) International Application Number: PCT/GB97/02212

(22) International Filing Date: 13 August 1997 (13.08.97)

(30) Priority Data:

9617302.6	17 August 1996 (17.08.96)	GB
9701417.9	24 January 1997 (24.01.97)	GB

(71) Applicant (for all designated States except US): ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BOYLE, Francis, Thomas [GB/GB]; Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). WARDLEWORTH, James, Michael [GB/GB]; Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

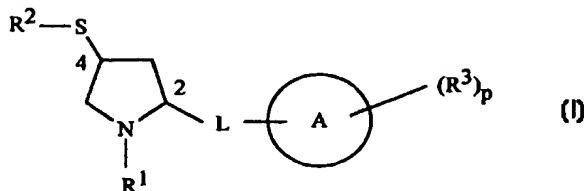
(74) Agent: TINSLEY, Rachel, Maria; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

(54) Title: 3-MERCAPTOPYRROLIDINES AS FARNESYL PROTEIN TRANSFERASE INHIBITORS



## (57) Abstract

The present invention relates to inhibitors of ras farnesylation of Formula (I) wherein: R<sup>1</sup> is for example H and further values as defined in the specification; R<sup>2</sup> is for example H and further values as defined in the specification; R<sup>3</sup> is for example H or a substituent having values as defined in the specification; p is 0-3 in which R<sup>3</sup> values can be the same or different; L is a linking moiety for example -CH<sub>2</sub>-NH- and further values as defined in the specification; A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms where the heteroatoms are independently selected from O, N and S; or a -S-S- dimer thereof when R<sup>2</sup>=H; or a N-oxide or a pharmaceutically-acceptable salt, prodrug or solvate thereof. Processes for their preparation, their use as therapeutic agents and pharmaceutical compositions containing them. A particular use is in cancer therapy.



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EE	Estonia						



### 3-MERCAPTOPYRROLIDINES AS FARNESYL PROTEIN TRANSFERASE INHIBITORS

This invention relates to compounds that inhibit farnesylation of mutant ras gene products through inhibition of the enzyme farnesyl-protein transferase (FPTase). The invention also relates to methods of manufacturing the compounds, pharmaceutical compositions and methods of treating diseases, especially cancer, which are mediated through farnesylation of ras.

Cancer is believed to involve alteration in expression or function of genes controlling cell growth and differentiation. Whilst not wishing to be bound by theoretical considerations the following text sets out the scientific background to ras in cancer. Ras genes are frequently mutated in tumours. Ras genes encode guanosine triphosphate (GTP) binding proteins which are believed to be involved in signal transduction, proliferation and malignant transformation. H-, K- and N-ras genes have been identified as mutant forms of ras (Barbacid M, Ann. Rev. Biochem. 1987, 56: 779-827). Post translational modification of ras protein is required for biological activity. Farnesylation of ras catalysed by FPTase is believed to be an essential step in ras processing. It occurs by transfer of the farnesyl group of farnesyl pyrophosphate (FPP) to a cysteine at the C-terminal tetrapeptide of ras in a structural motif called the CAAX box. After further post-translational modifications, including proteolytic cleavage at the cysteine residue of the CAAX box and methylation of the cysteine carboxyl, ras is able to attach to the cell membrane for relay of growth signals to the cell interior. In normal cells activated ras is believed to act in conjunction with growth factors to stimulate cell growth. In tumour cells it is believed that mutations in ras cause it to stimulate cell division even in the absence of growth factors (Travis J, Science 1993, 260: 1877-1878), possibly through being permanently in GTP activated form rather than cycled back to GDP inactivated form. Inhibition of farnesylation of mutant ras gene products will stop or reduce activation.

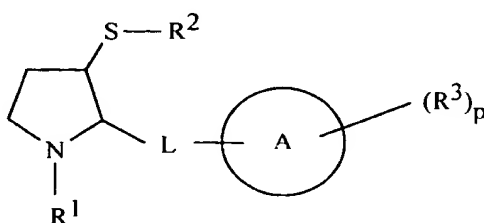
One class of known inhibitors of farnesyl transferase is based on farnesyl pyrophosphate analogues; see for example European patent application EP 534546 from Merck. Inhibitors of farnesyl transferase based on mimicry of the CAAX box have been reported. Reiss (1990) in Cell 62, 81-8 disclosed tetrapeptides such as CVIM (Cys-Val-Ile-Met). James (1993) in Science 260, 1937-1942 disclosed benzodiazepine based





peptidomimetic compounds. Lerner (1995) in J. Biol. Chem. 270, 26802 and Eisai in International Patent Application WO 95/25086 disclosed further peptidomimetic compounds based on Cys as the first residue. Bristol-Myers Squibb in European Patent Application EP 696593 disclosed for the first time farnesyl transferase inhibitors having a 4-sulfanylpyrrolidine residue in the first position. It is believed that there has been no disclosure of such compounds having a 3-sulfanyl pyrrolidine moiety in the first position.

According to one aspect of the present invention there is provided an inhibitor of ras farnesylation of Formula I



Formula I

10 wherein:

$R^1$  is selected from H;  $-C_{1-4}$ alkyl;  $-CO-C_{1-4}$ alkyl;  $-CO-O-C_{1-4}$ alkyl;  $-CO-O-C_{2-4}$ alkenyl;  $-C_{1-4}$ alkylene- $CONR^4R^5$  (wherein  $R^4$  and  $R^5$  are independently selected from H and  $C_{1-4}$ alkyl);  $-C_{1-4}$ alkylene- $COOR^6$  (wherein  $R^6$  is selected from H and  $C_{1-4}$ alkyl);  $-C_{1-3}$ alkylene-Ph and  $-CO-O(CH_2)_nPh$  wherein the phenyl groups in  $-C_{1-3}$ alkylene-Ph and  $-CO-O(CH_2)_nPh$  are optionally substituted by  $R^a$  and/or  $R^b$  and  $R^a$  and  $R^b$  are

independently selected from  $C_{1-4}$ alkyl, halogen, hydroxy,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkanoyl,  $C_{1-4}$ alkanoyloxy, amino,  $C_{1-4}$ alkylamino, di( $C_{1-4}$ alkyl)amino,  $C_{1-4}$ alkanoylamino, nitro, cyano, carboxy, carbamoyl,  $C_{1-4}$ alkoxycarbonyl, thiol,  $C_{1-4}$ alkylsulfanyl,  $C_{1-4}$ alkylsulfinyl,  $C_{1-4}$ alkylsulfonyl and sulfonamido; and  $n=0-4$ ;

20  $R^2$  is selected from H;  $-C_{1-4}$ alkyl;  $-COC_{1-4}$ alkyl; and  $-COOC_{1-4}$ alkyl; and  $-C_{1-3}$ alkylene-Ph optionally substituted on the phenyl ring by  $R^a$  and/or  $R^b$ ;

$R^3$  is selected from H; OH; CN;  $CF_3$ ;  $NO_2$ ;  $-C_{1-4}$ alkyl;  $-C_{1-4}$ alkylene- $R^7$ ;  $-C_{2-4}$ alkenylene- $R^7$ ;  $-C_{2-4}$ alkynylene- $R^7$ ;  $R^7$ ;  $OR^7$  (where  $R^7$  is selected from phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms

25 selected from O, N and S and any aryl ring in  $R^7$  is optionally substituted by  $R^a$  and/or  $R^b$ );  $C_{2-4}$ alkenyl; halogen;  $-(CH_2)_nCOOR^8$  (where  $n = 0-3$  and  $R^8$  represents H,  $C_{1-4}$ alkyl, or  $C_{2-4}$ alkenyl);  $-CONR^9R^{10}$  (where  $R^9$  and  $R^{10}$  independently represent H,  $C_{1-4}$ alkyl,



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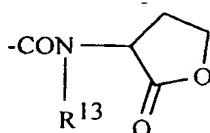
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C<sub>2</sub>-4alkenyl, -O-C<sub>1</sub>-4alkyl, -O-C<sub>2</sub>-4alkenyl or -C<sub>1</sub>-3alkylenePh (wherein Ph is optionally substituted by R<sup>a</sup> and R<sup>b</sup> as hereinabove defined); -CON(R<sup>11</sup>)OR<sup>12</sup> (where R<sup>11</sup> and R<sup>12</sup> independently represent H, C<sub>1</sub>-4alkyl or C<sub>2</sub>-4alkenyl);

a group of Formula II: -CONR<sup>13</sup>-CR<sup>13a</sup>R<sup>14</sup>-COOR<sup>17</sup>, (where R<sup>13</sup> and R<sup>13a</sup> are independently H or C<sub>1</sub>-4alkyl, R<sup>17</sup> is H or C<sub>1</sub>-6alkyl, R<sup>14</sup> is selected from the side chain of a lipophilic amino acid, carbamoylC<sub>1</sub>-4alkyl, N-(monoC<sub>1</sub>-4alkyl)carbamoylC<sub>1</sub>-4alkyl and N-(diC<sub>1</sub>-4alkyl)carbamoylC<sub>1</sub>-4alkyl) the group of Formula II having L or D configuration at the chiral alpha carbon in the corresponding free amino acid; a lactone of formula:

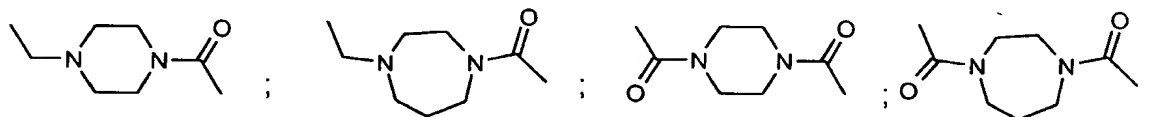


C<sub>1</sub>-4alkyl monosubstituted on carbon with =N-OH;

a group of Formula -X-R<sup>15</sup> (where X is selected from O, CO, CH<sub>2</sub>, S, SO, SO<sub>2</sub> and R<sup>15</sup> is selected from C<sub>1</sub>-6alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and any aryl ring in R<sup>15</sup> is optionally substituted by R<sup>a</sup> and/or R<sup>b</sup>;

p is 0-3 in which R<sup>3</sup> values can be the same or different;

L is a linking moiety selected from the following groups written from left to right in Formula I:



(wherein the piperazine and perhydro-1,4-diazepine rings are optionally substituted);  
 -CO-NR<sup>16</sup>-; -CH<sub>2</sub>-NR<sup>16</sup>-; -CH<sub>2</sub>S-; -CH<sub>2</sub>O-; -CH<sub>2</sub>-CHR<sup>16</sup>-; -CH=CR<sup>16</sup>-; -CH<sub>2</sub>NR<sup>16</sup>-T-;  
 -CH<sub>2</sub>NR<sup>16</sup>-SO<sub>2</sub>-; -CH<sub>2</sub>-NR<sup>16</sup>-CO-T<sup>1</sup>-; -CO-NR<sup>16</sup>-T-; -CH<sub>2</sub>S-T-; -CH<sub>2</sub>O-T- (where R<sup>16</sup> is selected from H, C<sub>1</sub>-4alkyl, C<sub>1</sub>-4alkylene-Z, -CO-C<sub>1</sub>-4alkylene-Z, -CO-C<sub>1</sub>-6alkyl, -COZ, Z and Z is selected from -O-C<sub>1</sub>-4alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and any aryl ring in R<sup>16</sup> is optionally substituted by R<sup>a</sup> and/or R<sup>b</sup> as hereinabove defined;



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where, T represents  $-(CH_2)_m-$  where m is 1-4 and T is optionally monosubstituted with any value of  $R^{16}$  other than H; and

where  $T^1$  represents  $-(CH_2)_{m^1}-$  wherein  $m^1$  is 0-4 and T is optionally monosubstituted with any value of  $R^{16}$  other than H);

5 A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms where the heteroatoms are independently selected from O, N & S;

or a -S-S- dimer thereof when  $R^2=H$ ; or a N-oxide thereof;

or a pharmaceutically acceptable salt, prodrug or solvate thereof.

10 In another aspect of the invention there is provided an inhibitor of ras farnesylation of Formula I

wherein:

$R^1$  is selected from H;  $-C_{1-4}alkyl$ ;  $-C_{1-3}alkylene-Ph$  optionally mono or di-substituted on Ph with substituents selected from  $C_{1-4}alkyl$ , halogen, OH,  $C_{1-4}alkoxy$ ,  $C_{1-4}alkanoyl$ ,

15  $C_{1-4}alkanoyloxy$ , amino,  $C_{1-4}alkylamino$ ,  $di(C_{1-4}alkyl)amino$ ,  $C_{1-4}alkanoylamino$ , nitro, cyano, carboxy, carbamoyl,  $C_{1-4}alkoxycarbonyl$ , thiol,  $C_{1-4}alkylsulfanyl$ ,  $C_{1-4}alkylsulfinyl$ ,  $C_{1-4}alkylsulfonyl$  and sulfonamido;  $-CO-C_{1-4}alkyl$ ;  $-CO-O-C_{1-4}alkyl$ ;  $-CO-O-C_{2-4}alkenyl$ ;  $-CO-O-(CH_2)_nPh$  optionally substituted on Ph as defined for substitution on Ph in  $R^1 = -C_{1-3}alkylene-Ph$  above and  $n=0-4$ ;

20  $-C_{1-4}alkylene-CONR^4R^5$  where  $R^4$  &  $R^5$  are independently selected from H and  $C_{1-4}alkyl$ ; and  $-C_{1-4}alkylene-COOR^6$  where  $R^6$  is selected from H,  $C_{1-4}alkyl$ ;

$R^2$  is selected from H;  $-C_{1-4}alkyl$ ;  $-C_{1-3}alkylene-Ph$  optionally substituted on Ph as defined for substitution on Ph in  $R^1 = -C_{1-3}alkylene-Ph$  above;  $-COC_{1-4}alkyl$ ; and  $-COOC_{1-4}alkyl$ ;

$R^3$  is selected from H; OH; CN;  $CF_3$ ;  $NO_2$ ;  $-C_{1-4}alkyl$ ;  $-C_{1-4}alkylene-R^7$  where  $R^7$  is

25 selected from phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and any aryl ring in  $R^7$  is optionally substituted as defined for substitution on the Ph group in  $R^1 = -C_{1-3}alkylene-Ph$  above;  $R^7$ ;

$C_{2-4}alkenyl$ ; halogen;  $-(CH_2)_nCOOR^8$  where  $n=0-3$  and  $R^8$  represents H,  $C_{1-4}alkyl$ , or  $C_{2-4}alkenyl$ ;  $-CONR^9R^{10}$  where  $R^9$  and  $R^{10}$  independently represent H,  $C_{1-4}alkyl$ ,

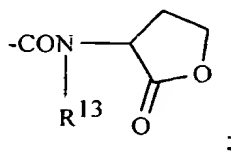
30  $C_{2-4}alkenyl$ ,  $-O-C_{1-4}alkyl$ ,  $-O-C_{2-4}alkenyl$ ,  $-C_{1-3}alkylenePh$  optionally substituted as



defined for this group for  $R^1$  above;  $-\text{CON}(R^{11})\text{OR}^{12}$  where  $R^{11}$  and  $R^{12}$  independently represent H,  $\text{C}_{1-4}$ alkyl and  $\text{C}_{2-4}$ alkenyl;

a group of Formula II,  $-\text{CONR}^{13}-\text{CHR}^{14}-\text{COOR}^{17}$ , where  $R^{13}$  is H or  $\text{C}_{1-4}$ alkyl,  $R^{17}$  is H or  $\text{C}_{1-6}$ alkyl,  $R^{14}$  is selected from the side chain of a lipophilic amino acid,

- 5 carbamoyl $\text{C}_{1-4}$ alkyl, N-(mono $\text{C}_{1-4}$ alkyl)carbamoyl $\text{C}_{1-4}$ alkyl and N-(di $\text{C}_{1-4}$ alkyl)carbamoyl $\text{C}_{1-4}$ alkyl, the group of Formula II having L or D configuration at the chiral alpha carbon in the corresponding free amino acid; a lactone of formula



$\text{C}_{1-4}$ alkyl monosubstituted on carbon with  $=\text{N}-\text{OH}$ ;

- 10 a group of Formula  $-\text{X}-\text{R}^{15}$  where X is selected from O, CO,  $\text{CH}_2$ , S, SO,  $\text{SO}_2$  and  $R^{15}$  is selected from  $\text{C}_{1-6}$ alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and any aryl ring in  $R^{15}$  is optionally substituted as defined for the Ph group in  $R^1 = -\text{C}_{1-3}$ alkylene-Ph; p is 0-3 in which  $R^3$  values can be the same or different;
- 15 **L** is a linking moiety selected from the following groups written from left to right in Formula I:
- $-\text{CO}-\text{NR}^{16}-$  where  $R^{16}$  is selected from H,  $\text{C}_{1-4}$ alkyl,  $\text{C}_{1-4}$ alkylene-Z,  $-\text{CO}-\text{C}_{1-4}$ alkylene-Z,  $-\text{CO}-\text{C}_{1-6}$ alkyl,  $-\text{COZ}$ , Z and Z is selected from  $-\text{O}-\text{C}_{1-4}$ alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from
- 20 O, N and S and any aryl ring in  $R^{16}$  is optionally substituted as defined for the Ph group in  $R^1 = -\text{C}_{1-3}$ alkylene-Ph;  $-\text{CH}_2-\text{NR}^{18}-$  where  $R^{18}$  represents any value defined for  $R^{16}$ ;  $-\text{CH}_2\text{S}-$ ;  $-\text{CH}_2\text{O}-$ ;  $-\text{CH}_2-\text{CHR}^{19}-$  where  $R^{19}$  represents any value defined for  $R^{16}$ ;  $-\text{CH}=\text{CR}^{20}-$  where  $R^{20}$  represents any value defined for  $R^{16}$ ;  $-\text{CH}_2\text{NR}^{21}-\text{T}-$  where  $R^{21}$  represents any value defined for  $R^{16}$ , T represents  $-(\text{CH}_2)_n-$  where n is 1-4 and T is optionally monosubstituted
- 25 with  $R^{22}$  where  $R^{22}$  represents any value for  $R^{16}$  other than H;  $-\text{CH}_2\text{NR}^{23}-\text{SO}_2-$  where  $R^{23}$  represents any value defined for  $R^{16}$ ;  $-\text{CH}_2-\text{NR}^{24}-\text{CO}-\text{T}-$  where  $R^{24}$  represents any value defined for  $R^{16}$ , T represents  $-(\text{CH}_2)_n-$  where n is 0-4 and T is optionally monosubstituted with  $R^{29}$  where  $R^{29}$  represents any value for  $R^{16}$  other than H;  $-\text{CO}-\text{NR}^{25}-\text{T}-$  where  $R^{25}$  represents any value defined for  $R^{16}$ , T represents  $-(\text{CH}_2)_n-$  where n is 1-4 and T is optionally



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- monosubstituted with  $R^{26}$  where  $R^{26}$  represents any value for  $R^{16}$  other than H;  $-\text{CH}_2\text{S}-\text{T}-$  where T represents  $-(\text{CH}_2)_n-$  where n is 1-4 and T is optionally monosubstituted with  $R^{27}$  where  $R^{27}$  represents any value for  $R^{16}$  other than H;  $-\text{CH}_2\text{O}-\text{T}-$  where T represents  $-(\text{CH}_2)_n-$  where n is 1-4 and T is optionally monosubstituted with  $R^{28}$  where  $R^{28}$  represents any value for  $R^{16}$  other than H;
- A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms where the heteroatoms are independently selected from O, N & S;
- or a -S-S- dimer thereof when  $R^2=\text{H}$ ; or a N-oxide thereof;
- 10 or an enantiomer, diastereoisomer, pharmaceutically acceptable salt, prodrug or solvate thereof.

In another aspect of the invention the group of Formula II is expanded to allow substitution of H by  $\text{C}_{1-4}\text{alkyl}$  at the  $\alpha$  carbon (to which  $R^{14}$  is attached) such that Formula II becomes  $-\text{CONR}^{13}-\text{CR}^{13a}\text{R}^{14}-\text{COOR}^{17}$  where  $R^{13a}$  represents H or  $\text{C}_{1-4}\text{alkyl}$  and other variable groups take any of the values (ranging from general to specific within the scope of Formula I) described herein.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only and references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. An analogous convention applies to other generic terms

The term "halogen" refers to fluorine, chlorine, bromine and iodine. The term "carbamoyl" refers to  $-\text{C}(\text{O})\text{NH}_2$ . The term "BOC" refers to tert-butyl-O-C(O)-. The term "allyl" refers to  $\text{CH}_2=\text{CH}-\text{CH}_2-$ . Bicyclic aryl and bicyclic heteroaryl rings refer to ring systems in which both rings of the bicyclic system are aromatic.

Examples of  $\text{C}_{1-6}\text{alkyl}$  include methyl, ethyl, propyl, isopropyl, *sec*-butyl, *tert*-butyl and pentyl; examples of  $\text{C}_{1-4}\text{alkyl}$  include methyl, ethyl, propyl, isopropyl, *sec*-butyl and *tert*-butyl; examples of  $\text{C}_{1-3}\text{alkyl}$  include methyl, ethyl, propyl and isopropyl; examples of  $\text{C}_{1-3}\text{alkylenePh}$  include benzyl, phenylethyl, phenylpropyl; examples of  $\text{C}_{1-4}\text{alkoxy}$  (also called  $-\text{O}-\text{C}_{1-4}\text{alkyl}$  herein) include methoxy, ethoxy and propoxy; examples of  $\text{C}_{1-4}\text{alkanoyl}$  include formyl, acetyl and propionyl; examples of  $\text{C}_{1-4}\text{alkanoyloxy}$  include



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- acetyloxy and propionyloxy; examples of **C<sub>1-4</sub>alkylamino** include methylamino, ethylamino, propylamino, isopropylamino, *sec*-butylamino and *tert*-butylamino; examples of **di-(C<sub>1-4</sub>alkyl)amino** include di-methylamino, di-ethylamino and N-ethyl-N-methylamino; examples of **C<sub>1-4</sub>alkanoylamino** include acetamido and propionylamino; examples of
- 5 **C<sub>1-4</sub>alkoxycarbonyl** include methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl; examples of **C<sub>1-4</sub>alkylsulfanyl** include methylsulfanyl, ethylsulfanyl, propylsulfanyl, isopropylsulfanyl, *sec*-butylsulfanyl and *tert*-butylsulfanyl; examples of **C<sub>1-4</sub>alkylsulfinyl** include methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, *sec*-butylsulfinyl and *tert*-butylsulfinyl; examples of **C<sub>1-4</sub>alkylsulfonyl** include methylsulfonyl, ethylsulfonyl,
- 10 propylsulfonyl, isopropylsulfonyl, *sec*-butylsulfonyl and *tert*-butylsulfonyl; examples of **-CO-C<sub>1-4</sub>alkyl** include formyl, acetyl, propionyl, butyryl and valeryl; examples of **-CO-O-C<sub>1-4</sub>alkyl** include ethyloxycarbonyl, propyloxycarbonyl and *tert*-butyloxycarbonyl (BOC); examples of **-CO-O-C<sub>2-4</sub>alkenyl** include allyloxycarbonyl and vinyloxycarbonyl; examples of **-CO-O-(CH<sub>2</sub>)<sub>n</sub>Ph** where n=0-4 include phenyloxycarbonyl, benzyloxycarbonyl,
- 15 phenylethyloxycarbonyl and phenylpropyloxycarbonyl; examples of **-C<sub>1-4</sub>alkylene-CONR<sup>4</sup>R<sup>5</sup>** include carbamoylmethyl, carbamoylethyl, N-methylcarbamoylethyl, N-methyl-N-ethylcarbamoylethyl; examples of **-C<sub>1-4</sub>alkylene-COOR<sup>6</sup>** include carboxymethyl, carboxyethyl, carboxypropyl, propionic acid methyl ester, acetic acid ethyl ester; examples of **C<sub>2-4</sub>alkenyl** include allyl and vinyl;
- 20 examples of **-O-C<sub>2-4</sub>alkenyl** include allyloxy and vinyloxy; examples of **lipophilic amino acids** include valine, leucine, isoleucine, methionine, phenylalanine, serine, threonine and tyrosine; examples of **carbamoylC<sub>1-4</sub>alkyl** include carbamoylmethyl, carbamoylethyl and carbamoylpropyl; examples of **N-(monoC<sub>1-4</sub>alkyl)carbamoylC<sub>1-4</sub>alkyl** include N-methylcarbamoylmethyl and N-ethylcarbamoylethyl; examples of **N-(diC<sub>1-4</sub>alkyl)carbamoyl-C<sub>1-</sub>**
- 25 **4alkyl** include N,N-dimethylcarbamoylethyl and N-methyl-N-ethylcarbamoylethyl; examples of **C<sub>1-4</sub>alkyl monosubstituted on carbon with =N-OH** include butyraldehyde oxime and propionaldehyde oxime; examples of **hydroxyC<sub>1-6</sub>alkyl** include hydroxymethyl, hydroxyethyl, hydroxypropyl, 2-hydroxypropyl, 2-(hydroxymethyl)propyl and hydroxypentyl;
- examples of **C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl** include methoxyethyl, ethoxyethyl and methoxybutyl;
- 30 examples of **C<sub>1-6</sub>alkylcarbonyl** include methylcarbonyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, *sec*-butylcarbonyl, *tert*-butylcarbonyl and pentylcarbonyl; examples of



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**hydroxyC<sub>1-6</sub>alkylcarbonyl** include hydroxyacetyl, hydroxypropionyl, hydroxybutyryl, 3-hydroxybutyryl and hydroxypentanoyl; examples of **C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkylcarbonyl** include methoxyacetyl, methoxypropionyl, ethoxybutyryl and butoxyacetyl; examples of **phenylC<sub>1-6</sub>alkyl** include benzyl, phenylethyl and phenylpropyl; examples of **-CO-C<sub>1-4</sub>alkyl-Ph** include phenylacetyl and phenylpropionyl; examples of **-CO-C<sub>1-4</sub>alkyl-heteroaryl** include 2-(3-pyridyl)-acetyl and 2-(3-thienyl)-acetyl; examples of **N-(C<sub>1-6</sub>alkyl)carbamoyl** include N-methyl-carbamoyl and N-ethyl-carbamoyl; examples of **N-(diC<sub>1-6</sub>alkyl)carbamoyl** include N,N-dimethylcarbamoyl and N-methyl-N-ethylcarbamoyl.

Examples of **5-10 membered monocyclic or bicyclic heteroaryl rings containing upto 5 heteroatoms selected from O,N and S** include the following:

Examples of 5- or 6-membered heteroaryl ring systems include imidazole, triazole, pyrazine, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole and thiophene. A 9 or 10 membered bicyclic heteroaryl ring system is an aromatic bicyclic ring system comprising a 6-membered ring fused to either a 5 membered ring or another 6 membered ring.

Examples of 5/6 and 6/6 bicyclic ring systems include benzofuran, benzimidazole, benzthiophene, benzthiazole, benzisothiazole, benzoxazole, benzisoxazole, pyridoimidazole, pyrimidoimidazole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline and naphthyridine.

Preferably monocyclic heteroaryl rings contain upto 3 heteroatoms and bicyclic heteroaryl rings contain upto 5 heteroatoms. Preferred heteroatoms are N and S, especially N. In general, attachment of heterocyclic rings to other groups is via carbon atoms. Suitable values of heterocycles containing only N as the heteroatom are pyrrole, pyridine, indole, quinoline, isoquinoline, imidazole, pyrazine, pyrimidine, purine and pteridine.

The term 'lipophilic amino acid' as used in this specification encompasses both natural and unnatural amino acids.

Examples of lipophilic amino acids which contribute their side chain (denoted R<sup>14</sup> within the definition of values for R<sup>3</sup>) include methionine, phenylglycine, phenylalanine, serine, leucine, isoleucine or valine. L configuration in the corresponding free amino acid is preferred. Examples of amino acid side chains are set out below. A preferred value for R<sup>14</sup> is -CH<sub>2</sub>-CH<sub>2</sub>-S-CH<sub>3</sub>. Further preferred values for R<sup>14</sup> are -CH<sub>2</sub>-OMe and -CH<sub>2</sub>-CH<sub>2</sub>-OMe. Some examples of amino acids and their side chains are given below:



Amino Acid	Side Chain
methionine	-CH <sub>2</sub> -CH <sub>2</sub> -S-CH <sub>3</sub>
phenylglycine	Ph
phenylalanine	-CH <sub>2</sub> -Ph
serine	-CH <sub>2</sub> OH or a C <sub>1-4</sub> alkyl (preferably methyl) ether thereof.
Leucine	-CH <sub>2</sub> -CHMe <sub>2</sub>
homoserine	-CH <sub>2</sub> -CH <sub>2</sub> -OH or a C <sub>1-4</sub> alkyl (preferably methyl) ether thereof.

When R<sup>17</sup> is H to give a COOH group in Formula II, and R<sup>14</sup> is -CH<sub>2</sub>-CH<sub>2</sub>-OH then a lactone can be formed where R<sup>17</sup> and R<sup>14</sup> together form part of a dihydrofuran-2-one heterocyclic ring. The same lactone can be formed for compounds of Formula III hereinbelow, where X<sup>4</sup> is OH and X<sup>3</sup> is H.

Preferably R<sup>1</sup> is selected from H; -CO-O-(CH<sub>2</sub>)<sub>n</sub>Ph optionally substituted on phenyl hereinabove defined; -CO-O-C<sub>2-4</sub>alkenyl; -CO-C<sub>1-4</sub>alkyl; -C<sub>1-4</sub>alkylene-CONR<sup>4</sup>R<sup>5</sup> where R<sup>4</sup> and R<sup>5</sup> are independently selected from H, C<sub>1-4</sub>alkyl.

10 Most preferably R<sup>1</sup> is hydrogen.

Preferably R<sup>2</sup> is selected from H and -CO-C<sub>1-4</sub>alkyl.

Most preferably R<sup>2</sup> is hydrogen.

Preferably L is selected from -CH<sub>2</sub>-NR<sup>16</sup>- and -CH<sub>2</sub>NR<sup>16</sup>-T.

Preferably A is selected from phenyl, naphthyl, pyridyl and thienyl.

15 Most preferably A is phenyl or naphthyl.

Preferably combinations of R<sup>3</sup> and p are selected from:

i) R<sup>3</sup> is selected from a group of Formula II, -C<sub>1-4</sub>alkylR<sup>7</sup>, -O-R<sup>7</sup> and R<sup>7</sup>; and p=1-3 with the proviso that at least one of R<sup>3</sup> is a group of the Formula II;

ii) p=0 with the proviso that A is naphthyl and L is -CH<sub>2</sub>NR<sup>16</sup>-T; and

20 iii) p=1 with the proviso that R<sup>3</sup> = a group of Formula II and A is phenyl or naphthyl.

Suitable pairs of values for R<sup>3</sup> when p=2 are: -COOMe, -CO.N(Me).OMe; NO<sub>2</sub>, -CO.N(Me).OMe; -COOMe, allyloxycarbonyl; -CO.N(Me).OMe, allyloxycarbonyl; allyloxycarbonyl, -CO.N(Me).O.CH<sub>2</sub>CH=CH<sub>2</sub>; OH, COOH; -COOMe, COOMe; Ph,



1

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3

4



-CO.N-Methionine methyl ester; Ph, -CO.N-Methionine; benzyl, -CO.N-Methionine methyl ester; benzyl, -CO.N-Methionine; benzyl, -CO.N-Methionine isopropyl ester; Ph, -CO.N $\alpha$ -Glutamine methyl ester; and Ph, -CO.N $\alpha$ -Glutamine.

Suitable values for L= CHNR<sup>16</sup> T include CH<sub>2</sub>.N(CO.CH<sub>2</sub>.CHMe<sub>2</sub>).CH<sub>2</sub>.CH<sub>2</sub>;

- 5 CH<sub>2</sub>.N(CH<sub>2</sub> CH<sub>2</sub> CH<sub>2</sub>OMe).CH<sub>2</sub>.CH<sub>2</sub>; CH<sub>2</sub>.N(CH<sub>2</sub>.*p*Ph.OMe).CH<sub>2</sub>.CH<sub>2</sub>;  
CH<sub>2</sub>.N(CO.CH<sub>2</sub>.CHMe<sub>2</sub>).CH<sub>2</sub>; CH<sub>2</sub>N(CO.CH<sub>2</sub>.CH<sub>2</sub>.CH<sub>2</sub>.Me).CH<sub>2</sub>;  
CH<sub>2</sub>N(CO.CH<sub>2</sub>.CHMe.CH<sub>2</sub>Me).CH<sub>2</sub>; CH<sub>2</sub>N(CO.CH<sub>2</sub>.CH<sub>2</sub>.OMe)CH<sub>2</sub>;  
CH<sub>2</sub>N(CO.CH<sub>2</sub>.pyridin-3-yl).CH<sub>2</sub>; CH<sub>2</sub>N(4-methoxybenzyl)CH<sub>2</sub>;  
CH<sub>2</sub>N(CO.CH<sub>2</sub>.CHMe<sub>2</sub>)CH<sub>2</sub>.CH<sub>2</sub>.CH(Ph); CH<sub>2</sub>N(CO.CH<sub>3</sub>)CH<sub>2</sub>.CH<sub>2</sub>.CH(Ph);  
10 CH<sub>2</sub>N(CO.CH<sub>2</sub>.CHMe<sub>2</sub>)CH<sub>2</sub>; CH<sub>2</sub>N(CO.CH<sub>3</sub>)CH<sub>2</sub>; CH<sub>2</sub>N(CO.CH<sub>2</sub>.CHMe<sub>2</sub>)CH<sub>2</sub>.CH(Ph);  
CH<sub>2</sub>N(CO.CH<sub>2</sub>.CMe<sub>3</sub>)CH<sub>2</sub>.CH(Ph); CH<sub>2</sub>N(CO.CH<sub>2</sub>.pyridin-3-yl)CH<sub>2</sub>.CH(Ph);  
CH<sub>2</sub>N(CO.1-hydroxy-6-methoxy-pyridin-3-yl)CH<sub>2</sub>.CH(Ph); CH<sub>2</sub>N(CO.CH<sub>2</sub> pyrid-3-yl)CH<sub>2</sub>CH(Ph); CH<sub>2</sub>N(CO.CH<sub>2</sub>CHMe<sub>2</sub>)CH<sub>2</sub>.CH<sub>2</sub>; CH<sub>2</sub>N(CO.CH<sub>2</sub>CMe<sub>3</sub>)CH<sub>2</sub>.CH<sub>2</sub>;  
CH<sub>2</sub>N(CO thiazol-2-yl)CH<sub>2</sub>CH<sub>2</sub>; CH<sub>2</sub>N(CO 1-oxido-6-hydroxypyridin-3-yl)CH<sub>2</sub>CH<sub>2</sub>;  
15 CH<sub>2</sub>N(CO.CH<sub>2</sub>pyridin-3-yl)CH<sub>2</sub>.CH<sub>2</sub> and CH<sub>2</sub>N(CO.4-methoxybenzyl)CH<sub>2</sub>.CH<sub>2</sub>.

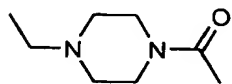
Preferred values for CH<sub>2</sub>NR<sup>16</sup>T include

CH<sub>2</sub>N(CO.CH<sub>2</sub>.CHMe<sub>2</sub>)CH<sub>2</sub>.CH(Ph); CH<sub>2</sub>N(CO.CH<sub>2</sub> pyridin-3-yl)CH<sub>2</sub>CH(Ph); CH<sub>2</sub>N(CO.1-hydroxy-6-hydroxypyridin-3-yl)CH<sub>2</sub>.CH(Ph); CH<sub>2</sub>N(CO thiazol-2-yl); CH<sub>2</sub>.CH<sub>2</sub>; and CH<sub>2</sub>N(CO.1-oxido-6-hydroxypyridin-3-yl) CH<sub>2</sub>.CH<sub>2</sub>.

- 20 Suitable values for L = -CH<sub>2</sub>NR<sup>16</sup> - include CH<sub>2</sub>NH; CH<sub>2</sub>NMe;  
CH<sub>2</sub>N(CO.CH<sub>2</sub>.CHMe<sub>2</sub>) and CH<sub>2</sub>N(CO.CH<sub>2</sub>.CH<sub>2</sub>.OMe). A preferred value for -CH<sub>2</sub>NR<sup>16</sup> is -CH<sub>2</sub>NH<sub>2</sub>-.

- When L is -CH<sub>2</sub>NR<sup>16</sup>-T- a suitable value for m is 1. When L is -CH<sub>2</sub>-NR<sup>16</sup>-CO-T'- a suitable value for m' is 1. When L is -CH<sub>2</sub>-NR<sup>16</sup>-T- a suitable value for m is 1. When L is  
25 -CH<sub>2</sub>-S-T- a suitable value for m is 1. When L is -CH<sub>2</sub>-O-T- a suitable value for m is 1.  
L is especially -CONH-, -CH<sub>2</sub>-NH-, -CH<sub>2</sub>NHSO<sub>2</sub>-, -CH<sub>2</sub>NHCO-.

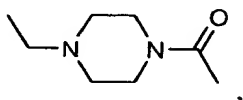
In another aspect L is of the formula



wherein the piperazine ring is optionally substituted by C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, phenoxyC<sub>1-4</sub>alkyl or heteroaryloxyC<sub>1-4</sub>alkyl.

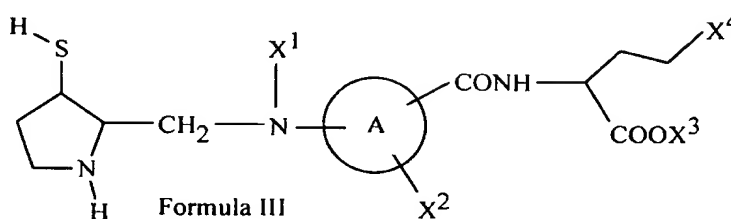


Preferably, when L is of the formula



5 A is naphthyl.

Preferred compounds of the invention are any of the formulae III, IV and V:



wherein:

10 X<sup>1</sup> is selected from H; C<sub>1</sub>-6alkyl; hydroxyC<sub>1</sub>-6alkyl, C<sub>1</sub>-6alkoxyC<sub>1</sub>-6alkyl; C<sub>1</sub>-6alkylcarbonyl; hydroxyC<sub>1</sub>-6alkylcarbonyl; C<sub>1</sub>-6alkoxyC<sub>1</sub>-6alkylcarbonyl;

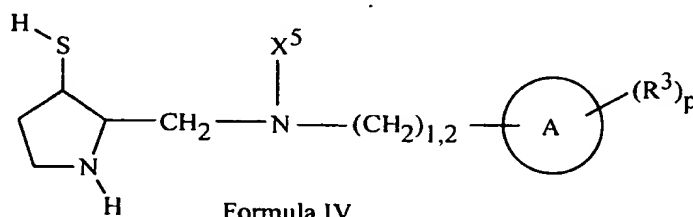
A is selected from phenyl, naphthyl or a 5-10 membered heterocyclic ring having upto 5 heteroatoms selected from O, N and S;

X<sup>2</sup> is selected from H; phenyl; phenylC<sub>1</sub>-6alkyl; a 5-6 membered heteroaryl ring containing  
15 upto 3 heteroatoms selected from O, N and S optionally linked to A by C<sub>1</sub>-6alkyl; and X<sup>2</sup> is optionally substituted on any ring by R<sup>a</sup> and/or R<sup>b</sup> as hereinabove defined;

X<sup>3</sup> is selected from H; C<sub>1</sub>-6alkyl;

X<sup>4</sup> is selected from C<sub>1</sub>-6alkylsulfanyl; C<sub>1</sub>-6alkylsulfinyl; C<sub>1</sub>-6alkylsulfonyl; carbamoyl; N-(C<sub>1</sub>-6alkyl)carbamoyl; N-(diC<sub>1</sub>-6alkyl)carbamoyl; and hydroxy or a C<sub>1</sub>-4alkyl ether thereof;

20



wherein:



A

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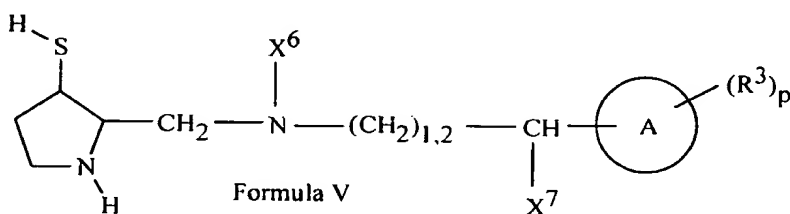
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$X^5$  is selected from  $C_{1-4}$ alkyloxy $C_{1-4}$ alkyl;  $-C_{1-4}$ alkylPh;  $-\text{CO}-C_{1-4}$ alkyl-Ph;  $-\text{CO}-C_{1-6}$ alkyl;  $-\text{CO}-C_{1-4}$ alkyl-heteroaryl where heteroaryl is a 5-10 membered heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and Ph or heteroaryl are optionally substituted by  $R^a$  and/or  $R^b$  as hereinabove defined;

5  $C_{1-4}$ alkyloxy $C_{1-4}$ alkyl;

A is naphthyl or a 10 membered heteroaryl ring having upto 5 heteroatoms selected from O, N and S;

$R^3$  and p are as defined above;



10 wherein:

$X^6$  has any value defined for  $X^5$  in ii) above;

$X^7$  is Ph optionally substituted by  $R^a$  and/or  $R^b$  as hereinabove defined;

A is Ph or naphthyl or a 5-10 membered heteroaryl ring having upto 5 heteroatoms selected  
15 from O, N and S;

$R^3$  and p are as defined above;

or a N-oxide, pharmaceutically acceptable salt, prodrug or solvate thereof.

A preferred values for compounds of the formula III include,

$X^1$  is selected from H and  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl;

20  $X^2$  is selected from H; phenyl and phenyl $C_{1-6}$ alkyl;

$X^4$  is  $C_{1-6}$ alkylsulfanyl; and

A is selected from phenyl and naphthyl.

Other preferred values for  $X^4$  are -OMe and the lactone which can be formed when  $X^4$  is OH and  $X^3$  is H.

25 A preferred value for compounds of the formula IV is p is 0.

Preferred values for compounds of the formula V include:

$X^7$  is phenyl;

A is phenyl; and



p is 0.

In another embodiment of the invention preferred values are set out below:

In compounds of Formula III:  $X^1$  is H or methoxyC<sub>1-4</sub>alkyl (especially H);  $X^2$  is H, phenyl, benzyl, phenethyl, 4-methylphenethyl or 4-methylphenylacetylene (especially benzyl);  $X^3$  is H or C<sub>1-4</sub>alkyl (especially H);  $X^4$  is C<sub>1-4</sub>alkylsulfanyl (especially methylsulfanyl); and A is phenyl. When A is a 6-membered aryl or heteroaryl ring then groups -NX<sup>1</sup>- and the substituent comprising X<sup>4</sup> are preferably in meta juxtaposition relative to each other; and X<sup>2</sup>, if present, is preferably positioned para relative to -NX<sup>1</sup>-. The chiral carbon to which -COOX<sup>3</sup> is attached is preferably in S configuration. The chiral carbons at the 2 and 3 positions of the pyrrolidine ring are preferably in R configuration.

In compounds of Formula IV:  $X^5$  is pyridylmethylcarbonyl, thiazolylcarbonyl, 1-oxido pyridylcarbonyl, -CO-C<sub>1-4</sub>alkyl (especially -CO-CH<sub>2</sub>-CHMe<sub>2</sub>) or -CH<sub>2</sub>-Ph-O-C<sub>1-4</sub>alkyl (especially -CH<sub>2</sub>-Ph-OMe); and A is phenyl or naphthyl and p is 0. The chiral carbons at the 2 and 3 positions of the pyrrolidine ring are preferably in R configuration. The attachment point for A relative to -(CH<sub>2</sub>)<sub>1,2</sub>- is preferably at the 1 position of naphthalene and the equivalent position for heterocyclic values for A (regardless of ring numbering conventions for heterocycles). A preferred value for -(CH<sub>2</sub>)<sub>1,2</sub>- is -(CH<sub>2</sub>)<sub>2</sub>-.

In compounds of Formula V:  $X^6$  is pyridylmethylcarbonyl, thiazolylcarbonyl, 1-oxido pyridylcarbonyl, -CO-C<sub>1-5</sub>alkyl (more preferably -CO-CH<sub>2</sub>-CHMe<sub>2</sub> or -CO-CH<sub>2</sub>-*t*-butyl, especially -CO-CH<sub>2</sub>-CHMe<sub>2</sub>) or -CH<sub>2</sub>-Ph-O-C<sub>1-4</sub>alkyl (especially -CH<sub>2</sub>-Ph-OMe);  $X^7$  is phenyl; and A is phenyl or naphthyl (especially phenyl) and p is 0. The chiral carbons at the 2 and 3 positions of the pyrrolidine ring are preferably in R configuration. A preferred value for -(CH<sub>2</sub>)<sub>1,2</sub>- is -CH<sub>2</sub>-.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of inhibiting FTPase. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic

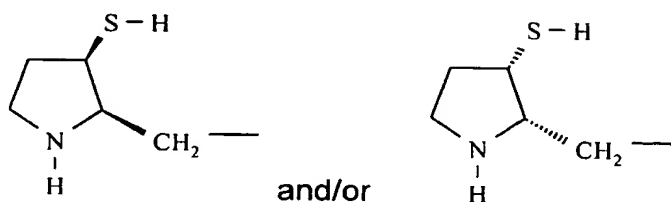




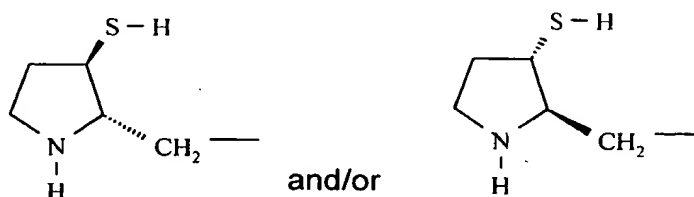
form. Similarly, inhibitory properties against FTPase may be evaluated using the standard laboratory techniques referred to hereinafter.

Preferably substituents on the 2 and 3 positions of the pyrrolidine ring in compounds of the Formula I are in the cis configuration.

5



Another suitable configuration is the trans configuration.



10

According to another aspect of the present invention there is provided any one of the following individual compounds or a pharmaceutically acceptable salt thereof:

(2S)-2-{2-benzyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester ;

15 (2S)-2-{2-benzyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid ;

(2S)-2-({2-phenyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester;

(2S)-2-({2-phenyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-phenylcarbonyl}-amino)-4-20 methylsulfanylbutyric acid;

(2S)-2-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-naphthalene-1-carbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester ;

(2S)-2-({3-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-naphthalene-1-carbonyl}-amino)-4-methylsulfanylbutyric acid ;



- (2S)-2-({-3-phenyl-5[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester;
- (2S)-2-({-3-phenyl-5[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid;
- 5 (cis)-2-[{N-(4-methoxybenzyl)-N-(naphthalen-1-ylmethylamino)-methyl]-pyrrolidine-3-thiol ;
- N-(naphthalen-1-ylmethyl)-N-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl]-pentanamide;
- N-(naphthalen-1-ylmethyl)-N-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl]-2-(pyridin-3-yl)-acetamide;
- 10 N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl]-3-methyl-N-(2-naphthalen-1-yl-ethyl)butyramide;
- N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-N-(2-naphthalen-1-yl-ethyl)-2-pyridin-3-yl-acetamide ;
- (cis)-2-{{(3-methoxypropyl)-(2-naphthalen-1-ylethyl)amino}methyl}-pyrrolidine-3-thiol;
- N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-2-(4-methoxy-phenyl)-N-(2-naphthalen-2-yl-ethyl)-acetamide;
- 15 (cis)-2-{{(2-(4-methoxyphenyl)ethyl)-(2-naphthalen-1-ylethyl)amino} methyl}-pyrrolidine-3-thiol;
- N-(2,2-diphenyl-ethyl)-N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-butylamide ;
- N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-2-yl-ethyl)-butylamide;
- 20 N-(2,2-diphenyl-ethyl)-N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-butylamide;
- (2S)-2-{3-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-(3-methoxy-propyl)-amino]-benzoylamino}-4-methylsulfanyl-butylric acid ;
- N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-1-yl-ethyl)-butylamide;
- 25 (2S)-4-carbamoyl-2-({2-phenyl-5-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-butylric acid;
- (2S)-4-carbamoyl-2-({2-phenyl-5-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-butylric acid methyl ester;
- 30 2-(3-pyridyl)-N-(2,2-diphenyl-ethyl)-N-(cis)-3-sulfanylpyrrolidin-2-ylmethyl)-acetamide;



6-methoxy-1-oxido-N-(2,2-diphenyl-ethyl)-N-(cis)-3-sulfanylpyrrolidin-2-ylmethyl)-pyridine-3-carboxamide;

N-(naphthyl-1-yl-ethyl)-N-[(cis)-3-sulfanylpyrrolidin-2yl-methyl]-thiazole-5-carboxamide;

6-methoxy-1-oxido-N-(naphthyl-1-yl-ethyl)-N-(cis)-3-sulfanylpyrrolidin-2-ylmethyl)-

5 pyridine-3-carboxamide;

(2S)-2-{2-benzyl-4-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanylbutyric acid;

(2S)-2-(2-methoxy-ethyl)-1-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-4-naphthoyl-piperazine;  
and

10 (2S)-2-{2-benzyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl)amino]-benzoylamino}-4-methylsulfanylbutyric acid;

(2S)-2-{2-benzyl-4-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl)amino]-benzoylamino}-4-methylsulfanylbutyric acid;

(2S)-2-{2-phenethyl-5-[(trans)-3-sulfanylpyrrolidin-2-ylmethylaminobenzoylamino]-4-

15 methylsulfanylbutyric acid;

(2S)-2-{phenethyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid;

(2S)-2-{2-benzyl-5-[(trans)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid;

20 (2S)-2-{2-(phenethyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino)-4-methylsulfanylbutyric acid;

(2S)-2-{2-(4-methylphenylethynyl)-4-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid;

(2S)-2-{2-benzyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-

25 methylsulfanylbutyric acid isopropyl ester;

(2S)-2-{2-benzyl-4-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;

(2S)-2-{2-benzyl-4-[(trans)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;

30 (2S)-2-{2-benzyl-5-[(trans)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;



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- (2S)-2-{2-phenyl-5-[(trans)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
- (2S)-2-{2-phenyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
- 5 (2S)-2-{2-benzyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
- (2S)-2-{2-(4-methylphenethyl)-4-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
- (2S)-2-{2-(4-methylphenylethynyl)-4-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-
- 10 benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
- (2S)-2-(2-methoxyethyl)-1-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl]-4-(naphth-1-yl)piperazine;
- (cis)-2-[N-isovaleryl-N-(2-(naphth-1-yl)ethyl)aminomethyl]-3-sulfanylpyrrolidine;
- (cis)-2-[N-(3-pyridylacetyl)-N-(naphth-1-yl)ethyl)aminomethyl]-3-sulfanylpyrrolidine;
- 15 (cis)-2-[N-(1-oxido-6-methoxypyridin-3-ylcarbonyl);
- (cis)-2-[N-(thiazol-5-ylcarbonyl) N-(naphth-1-yl)ethyl)aminomethyl]-3-sulfanylpyrrolidine;
- (2S)-2-[2-(4-fluorophenethyl)-4-[(cis)-3-sulfanyl]-pyrrolidin-2-ylmethylamino]benzoylamino]-4-methylsulfanylbutyric acid;
- methyl (2S)-2-[2-(4-fluorophenethyl)-4-[(cis)-3-sulfanylpyrrolidin-2-
- 20 ylmethylamino]benzoylamino]-4-methylsulfanylbutyrate; and
- (2S)-2-[2-(4-fluorophenethyl)-5-((2R,3R)-3-sulfanyl-pyrrolidin-2-ylmethylamino)benzoylamino]-4-methylsulfanylbutyric acid.

According to yet another aspect of the present invention there is provided any one of

25 the following individual compounds or a pharmaceutically acceptable salt thereof:

- (2S)-2-{2-Benzyl-5-[[2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester ;
- (2S)-2-{2-Benzyl-5-[[2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanylbutyric acid ;
- 30 (2S)-2-({2-phenyl-5-[[2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester;





- (2S)-2-({2-phenyl-5-([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino}-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid;
- (2S)-2-({3-([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino}-naphthalene-1-carbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester ;
- 5 (2S)-2-({3-([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino}-naphthalene-1-carbonyl)-amino)-4-methylsulfanylbutyric acid ;
- (2S)-2-({3-phenyl-5([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino}-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester;
- (2S)-2-({3-phenyl-5([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino}-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid;
- 10 (2R,3R)-2-[{N-(4-methoxybenzyl)-N-(naphthalen-1-ylmethyl)-amino}-methyl]-pyrrolidine-3-thiol ;
- N-(naphthalen-1-ylmethyl)-N-([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-pentanamide;
- N-(naphthalen-1-ylmethyl)-N-([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-2-(pyridin-3-yl)-acetamide ;
- 15 N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-N-(2-naphthalen-1-ylethyl)butyramide ;
- N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-N-(2-naphthalen-1-yl-ethyl)-2-pyridin-3-yl-acetamide ;
- 20 (2R,3R)-2-{[(3-Methoxypropyl)-(2-naphthalen-1-ylethyl)amino]methyl}-pyrrolidine-3-thiol;
- N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-2-(4-methoxy-phenyl)-N-(2-naphthalen-2-yl-ethyl)-acetamide ;
- (2R,3R)-2-{[(2-(4-Methoxyphenyl)ethyl)-(2-naphthalen-1-ylethyl)amino] methyl}-pyrrolidine-3-thiol ;
- 25 N-(2,2-Diphenyl-ethyl)-N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-butylamide ;
- N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-2-yl-ethyl)-butylamide ;
- N-(2,2-Diphenyl-ethyl)-N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-butylamide ;
- 30 (2S)-2-{3-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-(3-methoxy-propyl)-amino}-benzoylamino}-4-methylsulfanyl-butylamide ;



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N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-1-yl-ethyl)-butyramide ;

(2S)-4-carbamoyl-2-({2-phenyl-5-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-amino}-phenylcarbonyl)-amino)-butyric acid;

5 (2S)-4-carbamoyl-2-({2-phenyl-5-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-amino}-phenylcarbonyl)-amino)-butyric acid methyl ester;

2-(3-pyridyl)-N-(2,2-diphenyl-ethyl)-N-((2R,3R)-3-sulfanylpyrrolidin-2-ylmethyl)-acetamide;

6-methoxy-1-oxido-N-(2,2-diphenyl-ethyl)-N-((2R,3R)-3-sulfanylpyrrolidin-2-ylmethyl)-pyridine-3-carboxamide;

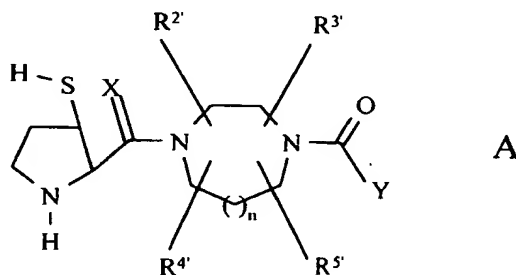
N-(naphthyl-1-yl-ethyl)-N-([2R,3R]-3-sulfanylpyrrolidin-2yl-methyl)-thiazole-5-carboxamide;

6-methoxy-1-oxido-N-(naphthyl-1-yl-ethyl)-N-((2R,3R)-3-sulfanylpyrrolidin-2-ylmethyl)-pyridine-3-carboxamide;

15 (2S)-2-{2-benzyl-4-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-amino}-benzoylamino}-4-methylsulfanyl-butyl-ic acid; and

(2S)-2-(2-methoxy-ethyl)-1-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-4-naphthoyl-piperazine.

20 In another aspect of the present invention there is provided a compound which inhibits farnesyl-protein transferase of the formula A:



25 wherein:

X is O or H<sub>2</sub>;



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3

4

5

n is 0 or 1;

t is 1 to 4;

$R^{2'}$ ,  $R^{3'}$ ,  $R^{4'}$ , and  $R^{5'}$  are independently selected from: H;  $C_1$ -alkyl, alkenyl, alkynyl, aryl, heterocycle,  $-CO-NR^{6'}R^{7'}$  or  $-CO-OR^{6'}$ , unsubstituted or substituted with one or more of:

5 1) aryl or heterocycle, unsubstituted or substituted with:

- a.  $C_{1-4}$ alkyl,
- b.  $(CH_2)_tOR^{6'}$ ,
- c.  $(CH_2)_tNR^{6'}R^{7'}$ ,
- d. halogen,

10 2)  $C_{3-6}$ cycloalkyl,

3)  $OR^{6'}$ ,

4)  $SR^{6'}$ ,  $S(O)R^{6'}$ ,  $SO_2R^{6'}$ ,

5)  $-NR^{6'}R^{7'}$ ,

6)  $-NR^{6'}-CO-R^{7'}$ ,

15 7)  $-NR^{6'}-CO-NR^{7'}R^{8'}$ ,

8)  $-O-CO-NR^{6'}R^{7'}$ ,

9)  $-O-CO-OR^{6'}$ ,

10)  $-O-NR^{6'}R^{7'}$ ,

11)  $-SO_2NR^{6'}R^{7'}$ ,

20 12)  $-NR^{6'}-SO_2-R^{7'}$ ,

13)  $-CO-R^{6'}$ , or

14)  $-CO-OR^{6'}$ ;

and any two of  $R^{2'}$ ,  $R^{3'}$ ,  $R^{4'}$ , and  $R^{5'}$  are optionally attached to the same carbon atom;

Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

25 1)  $C_1$ -alkyl, unsubstituted or substituted with:

- a.  $C_{1-4}$ alkoxy,
- b.  $NR^{6'}R^{7'}$ ,
- c.  $C_{3-6}$ cycloalkyl,
- d. aryl or heterocycle,

30 e. HO,

2) aryl or heterocycle,



- 21 -

- 3) halogen,
- 4)  $\text{OR}^{6'}$ ,
- 5)  $\text{NR}^{6'}\text{R}^{7'}$ ,
- 6) CN
- 7)  $\text{NO}_2$ , or
- 8)  $\text{CF}_3$ ;

$\text{R}^{6'}$ ,  $\text{R}^{7'}$  and  $\text{R}^{8'}$  are independently selected from: H;  $\text{C}_{1-4}$ alkyl,  $\text{C}_{3-6}$ cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

- 10 a)  $\text{C}_{1-4}$ alkoxy,
- b) aryl or heterocycle,
- c) halogen,
- d) HO,
- e)  $-\text{CO}-\text{R}^{9'}$ ,
- 15 f)  $-\text{SO}_2\text{R}^{9'}$ , or
- g)  $\text{NRR}^1$ , wherein

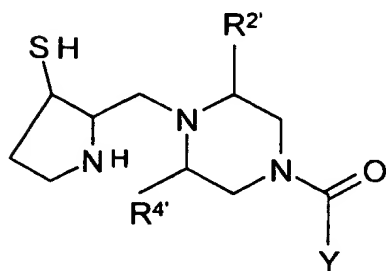
$\text{R}^{6'}$  and  $\text{R}^{7'}$  may be joined in a ring, and

$\text{R}^{7'}$  and  $\text{R}^{8'}$  may be joined in a ring;

20  $\text{R}^{9'}$  is  $\text{C}_{1-4}$ alkyl or aralkyl;

or a optical isomer, disulfide or pharmaceutically acceptable salt thereof.

A preferred subclass of the formula A is:



25

wherein  $\text{R}^{2'}$  and  $\text{R}^{4'}$  are independently hydrogen and Y is  $\text{C}_{1-4}$ alkyl, phenyl or a 5 or 6 membered heteroaryl ring containing upto 3 heteroatoms selected from N, O and S or of the





formula -C<sub>1-4</sub>alkyl OR<sup>10'</sup> wherein R<sup>10'</sup> is C<sub>1-4</sub>alkyl, phenyl or 5 or 6-membered heteroaryl containing upto 3 heteroatoms selected from N, O and S. Preferably R<sup>10'</sup> is C<sub>1-4</sub>alkyl.

Preferably Y is naphthyl.

The aspect of the invention relating to Formula A involves compounds related to those disclosed PCT patent application WO 95/00497 (Graham et al.); see the complete specification and claim 1 in particular. Formula A above is based on Formula A in WO 95/00497 (Graham et al.) but with the 3-sulfanylpyrrolidine moiety of the present invention replacing the cysteine-like moiety on the left hand side of Formula A in WO 95/00497 (Graham et al.). Optionally the nitrogen and/or thiol atoms in the pyrrolidine moiety of Formula A may be substituted by taking the values for R<sup>1</sup> and R<sup>2</sup> in Formula I as set out herein. Compounds within the scope of Formula A may be prepared by a skilled person using the synthetic details in WO 95/00497 (Graham et al.) combined with the present specification. Preferred compounds for this aspect of the invention correspond to those set out in claims 6-12 of WO 95/00497 (Graham et al.) but with the 3-sulfanylpyrrolidin-2-yl-methyl moiety of the present invention replacing the HS-CH<sub>2</sub>-CH(NH<sub>2</sub>)-CH- moiety on the left hand side of the relevant compounds attached to the piperazine ring as drawn out in the claims. A preferred compound is (2S)-2-(2-methoxy-ethyl)-1-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-4-naphthoyl-piperazine; see Example 7 herein.

Compounds of Formula I and III-V may form salts which are within the ambit of the invention. Pharmaceutically acceptable salts are preferred although other salts may be useful in, for example, isolating or purifying compounds.

When the compound contains a basic moiety it may form pharmaceutically acceptable salts with a variety of inorganic or organic acids, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. A suitable pharmaceutically-acceptable salt of the invention when the compound contains an acidic moiety is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a pharmaceutically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.



Solvates, for example hydrates, are also within the ambit of the invention and may be prepared by generally known methods.

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

- 5 a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);
- 10 c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

Examples of pro-drugs include *in vivo* hydrolysable esters of a compound of the Formula I. An *in vivo* hydrolysable ester of a compound of the formula (I) containing  
15 carboxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid. Suitable pharmaceutically-acceptable esters for carboxy include C<sub>1</sub>-6alkoxymethyl esters for example methoxymethyl, C<sub>1</sub>-6alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C<sub>3</sub>-8cycloalkoxycarbonyloxyC<sub>1</sub>-6alkyl esters for example 1-cyclohexylcarbonyloxyethyl;  
20 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C<sub>1</sub>-6alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

According to another aspect of the invention there is provided a pharmaceutical composition comprising a compound as defined in Formula I or an individual compound  
25 listed above together with a pharmaceutically acceptable diluent or carrier. A preferred pharmaceutical composition is in the form of a tablet.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams,  
30 ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation



(for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures  
5 using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium  
10 carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the  
15 gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with  
20 water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation  
25 products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example  
30 heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or



condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening  
5 agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and  
10 flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or  
15 wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil,  
20 or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene  
25 sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

30 The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using





one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

5           Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions  
10 or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30 $\mu$  or much less,  
15 the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

20           Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

25           For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the  
30 particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active



agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in 5 Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known 10 principles of medicine. As mentioned above, compounds of the Formula I are useful in treating diseases or medical conditions which are due alone or in part to the effects of farnesylation of ras.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg 15 per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however 20 preferred.

Compounds of this invention may be useful in combination with known anti-cancer and cytotoxic agents. If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent within its approved dosage range. Sequential use is 25 contemplated when a combination formulation is inappropriate.

According to another aspect of the invention there is provided a compound of Formula I, or a pharmaceutically-acceptable salt thereof, for use as a medicament.

According to another aspect of the invention there is provided a compound of Formula I, or a pharmaceutically-acceptable salt thereof, for use in preparation of a medicament for 30 treatment of a disease mediated through farnesylation of ras.

40

According to another aspect of the present invention there is provided a method of treating ras mediated diseases, especially cancer, by administering an effective amount of a compound of Formula I, or a pharmaceutically-acceptable salt thereof, to a mammal in need of such treatment.

- 5 Diseases or medical conditions may be mediated alone or in part by farnesylated ras. A particular disease of interest is cancer. Specific cancers of interest include:
- carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin;
  - hematopoietic tumors of lymphoid lineage, including acute lymphocytic
  - 10 leukemia, B-cell lymphoma and Burkett's lymphoma;
  - hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia;
  - tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;
  - and
  - 15 - other tumors, including melanoma, seminoma, teratocarcinoma, neuroblastoma and glioma.
- 511

The compounds of Formula I are especially useful in treatment of tumors having a high incidence of ras mutation, such as colon, lung, and pancreatic tumors. By the administration of a composition having one (or a combination) of the compounds of this

20 invention, development of tumors in a mammalian host is reduced.

Compounds of Formula I may also be useful in the treatment of diseases other than cancer that may be associated with signal transduction pathways operating through Ras, e.g., neuro-fibromatosis.

Compounds of Formula I may also be useful in the treatment of diseases

25 associated with CAAX-containing proteins other than Ras (e.g., nuclear lamins and transducin) that are also post-translationally modified by the enzyme farnesyl protein transferase.

Although the compounds of the Formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required

30 to inhibit the effects of activation of ras by farnesylation. Thus, they are useful as

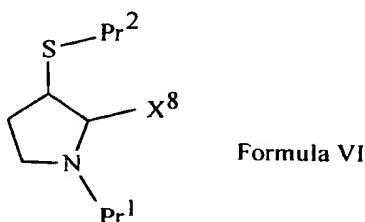
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pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

According to another aspect of the invention there is provided a process for preparing compounds Formula I as defined above which comprises deprotecting a compound of

5 Formula VI:



wherein  $\text{X}^8$  represents the right hand side of the Formula I,  $\text{Pr}^1$  is H or an amino protecting group,  $\text{Pr}^2$  is H or a thio protecting group and any functional groups in  $\text{X}^8$  are optionally protected with the proviso that there is at least one protecting group and optionally, if desired,

10 converting the product thus obtained into a pharmaceutically acceptable salt thereof.

Compounds outside the scope of Formula I having a 4-sulfanyl pyrrolidine moiety (compared with the 3-sulfanyl pyrrolidine moiety of the present invention) are known as intermediates in carbapenem side chain synthesis. The reader is referred to the following publications in this regard in respect of background synthetic details for assistance in

15 compound preparation: Matsumura, *Heterocycles* (1995), 41,

147-59; European patent application EP 590885 (Zeneca; Betts *et al*); European patent application EP 592167 (Zeneca; Siret); European patent application EP 562855 (Zeneca; Jung *et al*); International patent application WO 92/17480 (Imperial Chemical Industries; Betts *et al*); European patent application EP 508682 (Imperial Chemical Industries; Betts

20 *et al*); European Patent Application EP 280771 (Fujisawa Pharmaceutical, Murata *et al*); and International patent application WO 92/17479 (Imperial Chemical Industries; Betts *et al*).

A compound of the invention, or a salt thereof, may be prepared by any process known to be applicable to the preparation of such compounds or structurally related compounds. Such processes are illustrated by the following representative schemes in which

25 variable groups have any of the meanings defined for Formula I unless stated otherwise. Functional groups may be protected and deprotected using conventional methods. For examples of protecting groups such as amino and carboxylic acid protecting groups (as well as means of formation and eventual deprotection), see T.W. Greene and P.G.M. Wuts,





"Protective Groups in Organic Synthesis", Second Edition, John Wiley & Sons, New York, 1991. Note abbreviations used have been listed immediately before the Examples below.

Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms).

Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (e.g. isopropyl, *t*-butyl); lower alkoxy lower alkyl groups (e.g. methoxymethyl, ethoxymethyl, isobutoxymethyl; lower aliphatic acyloxy lower alkyl groups, (e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (e.g. 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (e.g. *p*-methoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (e.g. trimethylsilyl and *t*-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (e.g. trimethylsilylethyl); and (2-6C)alkenyl groups (e.g. allyl and vinyloethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, metal- or enzymically-catalysed hydrolysis.

Examples of hydroxy protecting groups include lower alkenyl groups (e.g. allyl); lower alkanoyl groups (e.g. acetyl); lower alkoxycarbonyl groups (e.g. *t*-butoxycarbonyl); lower alkenyloxycarbonyl groups (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzoyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *o*-nitrobenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl); tri lower alkyl/arylsilyl groups (e.g. trimethylsilyl,



*t*-butyldimethylsilyl, *t*-butyldiphenylsilyl); aryl lower alkyl groups (e.g. benzyl) groups; and triaryl lower alkyl groups (e.g. triphenylmethyl).

Examples of amino protecting groups include formyl, aralkyl groups (e.g. benzyl and substituted benzyl, e.g. *p*-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-*p*-anisylmethyl and furylmethyl groups; lower alkoxy carbonyl (e.g. *t*-butoxy carbonyl); lower alkenyloxy carbonyl (e.g. allyloxy carbonyl); aryl lower alkoxy carbonyl groups (e.g. benzyloxy carbonyl, *p*-methoxybenzyloxy carbonyl, *o*-nitrobenzyloxy carbonyl, *p*-nitrobenzyloxy carbonyl; trialkylsilyl (e.g. trimethylsilyl and *t*-butyldimethylsilyl); alkylidene (e.g. methylidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base, metal- or enzymically-catalysed hydrolysis, or photolytically for groups such as *o*-nitrobenzyloxy carbonyl, or with fluoride ions for silyl groups.

Examples of thiol protecting groups include aryl lower alkyl (e.g. benzyl, *p*-methoxybenzyl and *p*-nitrobenzyl); diphenylmethyl; triphenylmethyl; lower alkanoyl (e.g. acetyl); benzoyl lower alkoxy carbonyl (e.g. *tert*-butoxy carbonyl); benzyloxy carbonyl; and *tert*-butyl.

Examples of protecting groups for amide groups include aralkoxymethyl (e.g. benzyloxymethyl and substituted benzyloxymethyl); alkoxymethyl (e.g. methoxymethyl and trimethylsilylethoxymethyl); tri alkyl/arylsilyl (e.g. trimethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl); tri alkyl/arylsilyloxy methyl (e.g. *t*-butyldimethylsilyloxy methyl, *t*-butyldiphenylsilyloxy methyl); 4-alkoxyphenyl (e.g. 4-methoxyphenyl); 2,4-di(alkoxy)phenyl (e.g. 2,4-dimethoxyphenyl); 4-alkoxybenzyl (e.g. 4-methoxybenzyl); 2,4-di(alkoxy)benzyl (e.g. 2,4-di(methoxy)benzyl); and alk-1-enyl (e.g. allyl, but-1-enyl and substituted vinyl e.g. 2-phenylvinyl).

Aralkoxymethyl, groups may be introduced onto the amide group by reacting the latter group with the appropriate aralkoxymethyl chloride, and removed by catalytic hydrogenation. Alkoxymethyl, tri alkyl/arylsilyl and tri alkyl/silyloxy methyl groups may be introduced by reacting the amide with the appropriate chloride and removing with acid; or in the case of the silyl containing groups, fluoride ions. The alkoxyphenyl and alkoxybenzyl



groups are conveniently introduced by arylation or alkylation with an appropriate halide and removed by oxidation with ceric ammonium nitrate. Finally alk-1-enyl groups may be introduced by reacting the amide with the appropriate aldehyde and removed with acid.

Compounds of Formula I in which L represents  $-\text{CO}-\text{NR}^{16}-$  may be prepared by forming an amide bond between compounds 1 and 2 as outlined in Scheme 1. Compounds of Formula I in which L represents  $-\text{CO}-\text{NR}^{16}-\text{T}-$  may be prepared by an analogous procedure. Suitable coupling conditions include the following.

- i) Use of EEDQ at ambient temperature in an organic solvent (e.g. dichloromethane, methanol).
- 10 ii) Use of oxalyl chloride in an organic solvent (e.g.  $\text{CH}_2\text{Cl}_2$ ), DMF in a catalytic amount, in the presence of an organic base (e.g. NMM, triethylamine, DMAP) at  $0^\circ\text{C}$  to ambient temperature for 0.5-16h.
- iii) Use of EDC/ HOBt in an organic solvent (e.g. DMF,  $\text{CH}_2\text{Cl}_2$ ).
- iv) Use of DCCI/ HOBt in an organic solvent (e.g. DMF,  $\text{CH}_2\text{Cl}_2$ ) in the presence  
15 of an organic base (e.g. triethylamine).
- v) Use of mixed anhydride reactions under standard conditions, for example isopropylchloroformate in an organic solvent (e.g. DMF, DMA, dichloromethane) in the presence of an organic base (e.g. NMM, DMAP, triethylamine).
- vi) Via an active ester under standard conditions e.g. pentafluorophenyl ester in an  
20 organic solvent (e.g. dichloromethane) in the presence of an organic base (e.g. triethylamine).
- vii) Via an acid chloride under standard conditions e.g. using thionyl chloride and heat for about 150min followed by an organic base (e.g. triethylamine) in the presence of an organic solvent (e.g. acetonitrile).

Compounds of Formula I in which L represents  $-\text{CH}_2\text{NR}^{16}-$ ,  $-\text{CH}_2\text{O}-$  or  $-\text{CH}_2\text{S}-$  may be prepared as outlined in Scheme 2. LG represents a leaving group (e.g. mesyloxy, tosyloxy, halogen) and X represents S, O or  $\text{NR}^{16}$ . Suitable coupling conditions include the following.

- i) Use of an inorganic base (e.g.  $\text{NaHCO}_3$ , NaH,  $\text{K}_2\text{CO}_3$ , butyllithium) in an organic solvent (e.g. THF, DMF, DMSO) and a temperature of about  $65^\circ$  to  $150^\circ\text{C}$
- 30 ii) Use of an organic base (e.g. triethylamine, DMAP) in an organic solvent (e.g. THF, dichloromethane, DMA, DMF) at a temperature range of room temperature -  $150^\circ\text{C}$



iii) Use of an inorganic base (e.g. KOH, NaOH,  $K_2CO_3$ ) in an aqueous (e.g. water) and organic solvents (e.g. dichloromethane) in a 2 phase system, optionally in the presence of a phase transfer catalyst (e.g. tetrabutylammoniumbromide).

Compounds of Formula I in which L represents  $-CH=CR^{16}-$  may be prepared using a Wittig reaction as outlined in Scheme 3. Suitable reaction conditions include the following.

i) Use of a base (e.g. potassium carbonate, metal hydride, metal alkoxide) in the presence of an organic solvent (e.g. THF, toluene, DMSO) optionally in the presence of an aqueous solvent (2-phase system) and optionally in the presence of a catalyst complexing agent which solubilises alkali metal ions in non-polar solvents such as 1,4,7,10,13-pentaoxacyclopentadecane (also called 15-Crown-5) or 1,4,7,10,13,16-hexaoxacyclooctadecane (also called 18-Crown-6).

Compounds of Formula I in which L represents  $-CH_2-NR^{16}-$  may be prepared as outlined in Scheme 4 by coupling aldehyde (2) with compound 4. Suitable coupling conditions include the following.

i) Use of a reducing agent (e.g.  $NaCNBH_3$ ,  $BH_3$ , hydrogen plus catalyst,  $LiHBEt_3$ , di-isobutyl-aluminiumhydride, lithium aluminium hydride, sodium borohydride) in the presence of a suitable solvent e.g. ethanol and acetic acid.

Aldehyde (2) may be prepared by oxidation of the corresponding alcohol (1) under suitable conditions such as use of an oxidising agent (e.g. TPAP, NMM-O) in the presence of an organic solvent (e.g. acetonitrile, dichloromethane) at room temperature. Other suitable oxidising agents include chromium oxide, pyridinium chlorochromate, pyridinium dichromate, sodium dichromate, pyridine sulfur trioxide complex and sodium hypochlorite.

Aldehyde (2) may also be prepared by reduction of the corresponding ester (1) under standard conditions using for example diisobutyl-aluminium hydride. Alternatively, aldehyde (2) may be prepared by reducing the appropriate N-methoxy-N-methylcarboxamide with a strong reducing agent such as lithium aluminum hydride.

Compounds of Formula I in which L represents  $-CH_2-NR^{16}-T-$ ,  $-CH_2-O-T-$  or  $-CH_2-S-T-$  may be prepared as outlined in Scheme 5 in which LG represents a leaving group (e.g. mesyloxy, tosyloxy, halogen) and X represents O, S or  $NR^{16}$ . Suitable coupling





conditions are as outlined above in relation to Scheme 2. Optionally the positions of LG and XH in compounds 1 & 2 in Scheme 5 can be reversed to give the same end product.

Compounds of Formula I in which L represents  $-\text{CH}_2\text{-NR}^{16}\text{-SO}_2\text{-}$  may be prepared as outlined in Scheme 6. Compounds 1 & 2 may be coupled under standard conditions such as the following.

- i) Use of an organic base (e.g. di-isopropyl-ethylamine, triethylamine, 4-methyl-morpholine) in the presence of an organic solvent (e.g. dichloromethane) at a temperature range of  $0^\circ\text{-}40^\circ\text{C}$
- ii) Use of an inorganic base (e.g. potassium carbonate) in the presence of an organic solvent (e.g. DMF) at a temperature range of  $0^\circ\text{-}150^\circ\text{C}$

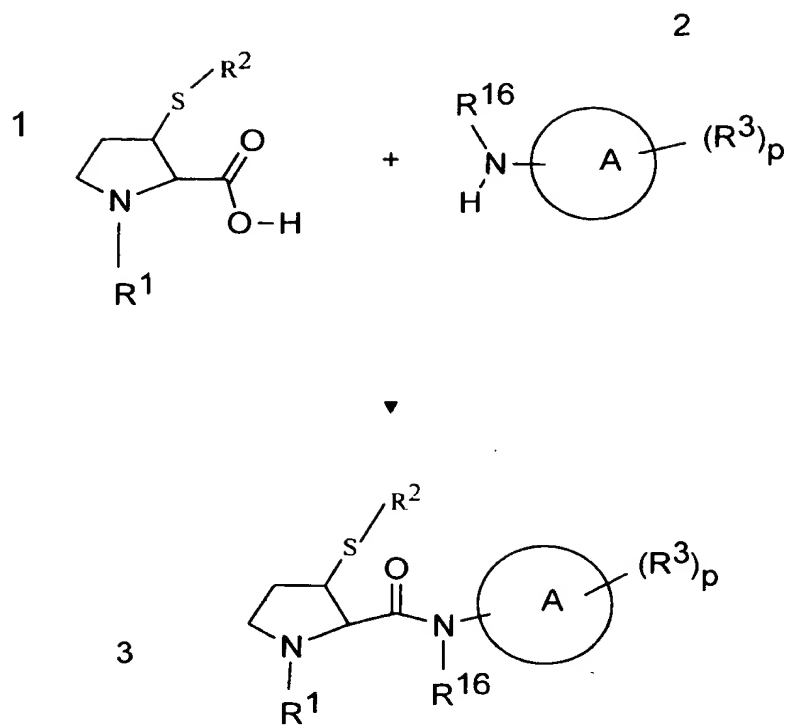
Compounds of Formula I in which L represents  $-\text{CH}_2\text{-NR}^{16}\text{-CO-T-}$  may be prepared as outlined in Scheme 7. Compounds 1 & 2 may be coupled under standard conditions such as described above for  $\text{L} = -\text{CO-NR}^{16}\text{-}$ .

Compounds of Formula I in which L represents  $-\text{CH}_2\text{-CHR}^{16}\text{-}$  may be prepared by reduction of compounds of the type set out as compound 3 in Scheme 3. Reduction is carried out under standard conditions with standard reagents for example using hydrogenation in the presence of a catalyst such as palladium on charcoal at ambient temperature.

Compounds of the formula I in which L represents  $-\text{CH}_2\text{NR}^{16}\text{-}$ ,  $-\text{CONR}^{16}\text{-}$ ,  $\text{CH}_2\text{N(R}^{16})\text{-T-}$  or  $-\text{CH}_2\text{N(R}^{16})\text{COT-}$  wherein  $\text{R}^{16}$  is not hydrogen, may be prepared from the appropriate compound of the formula I wherein  $\text{R}^{16}$  is hydrogen by introducing the appropriate  $\text{R}^{16}$  by acylation, alkylation etc. For example, by using similar methods to those disclosed in the specific examples.

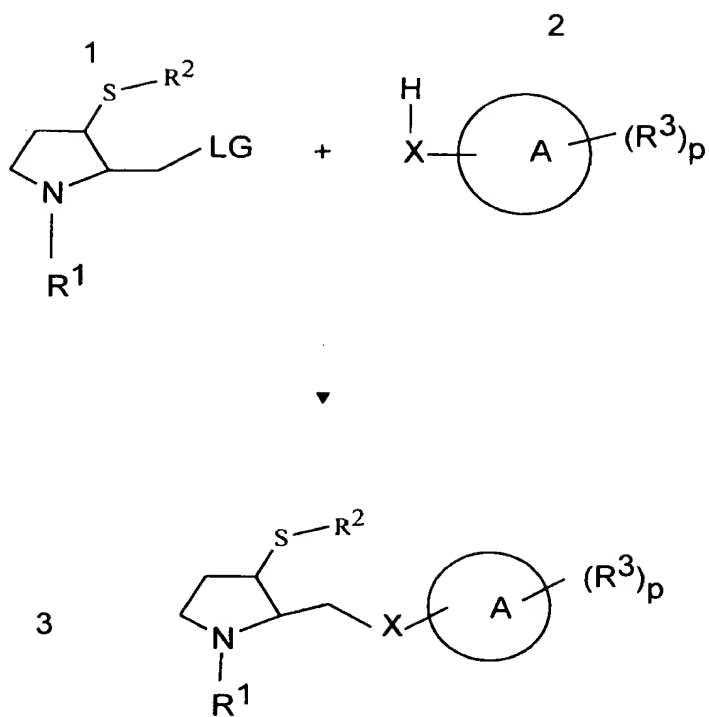


## Scheme 1



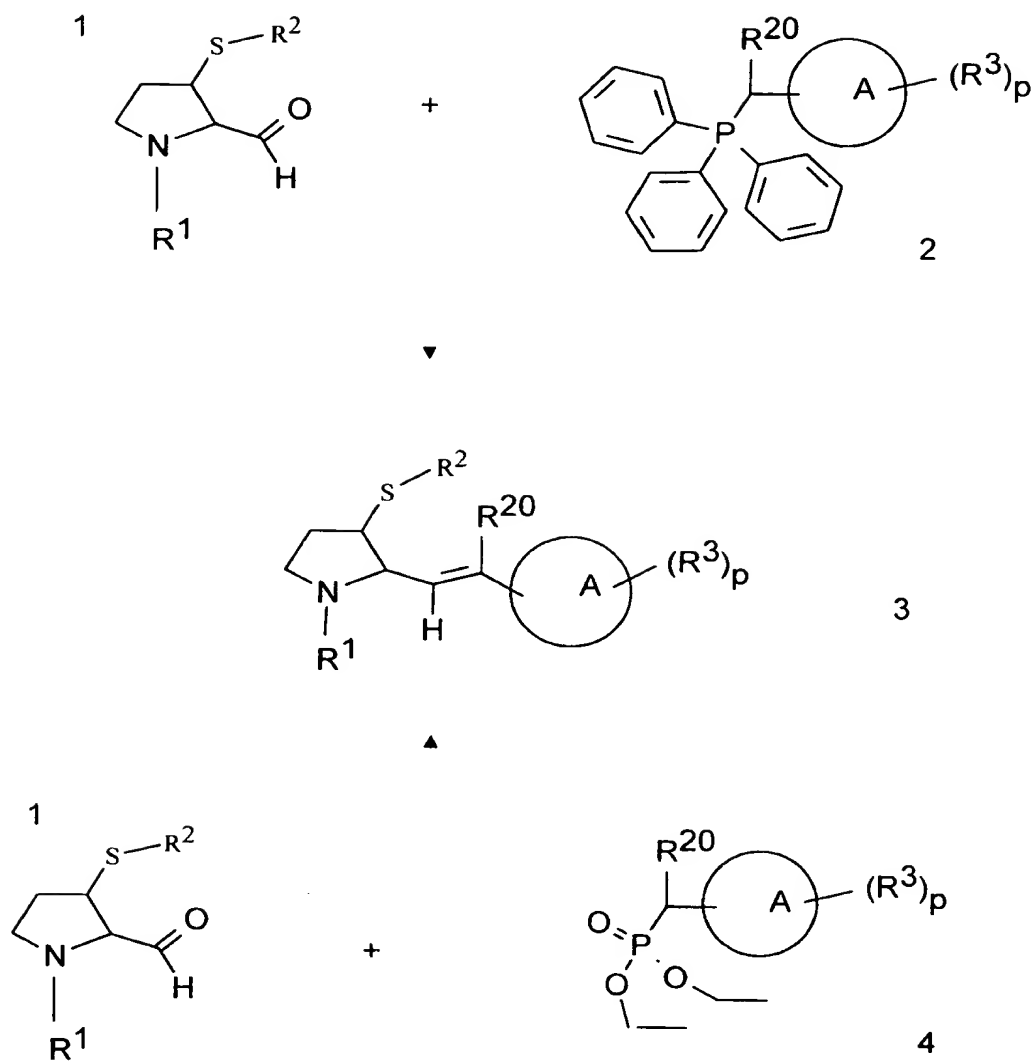


## Scheme 2





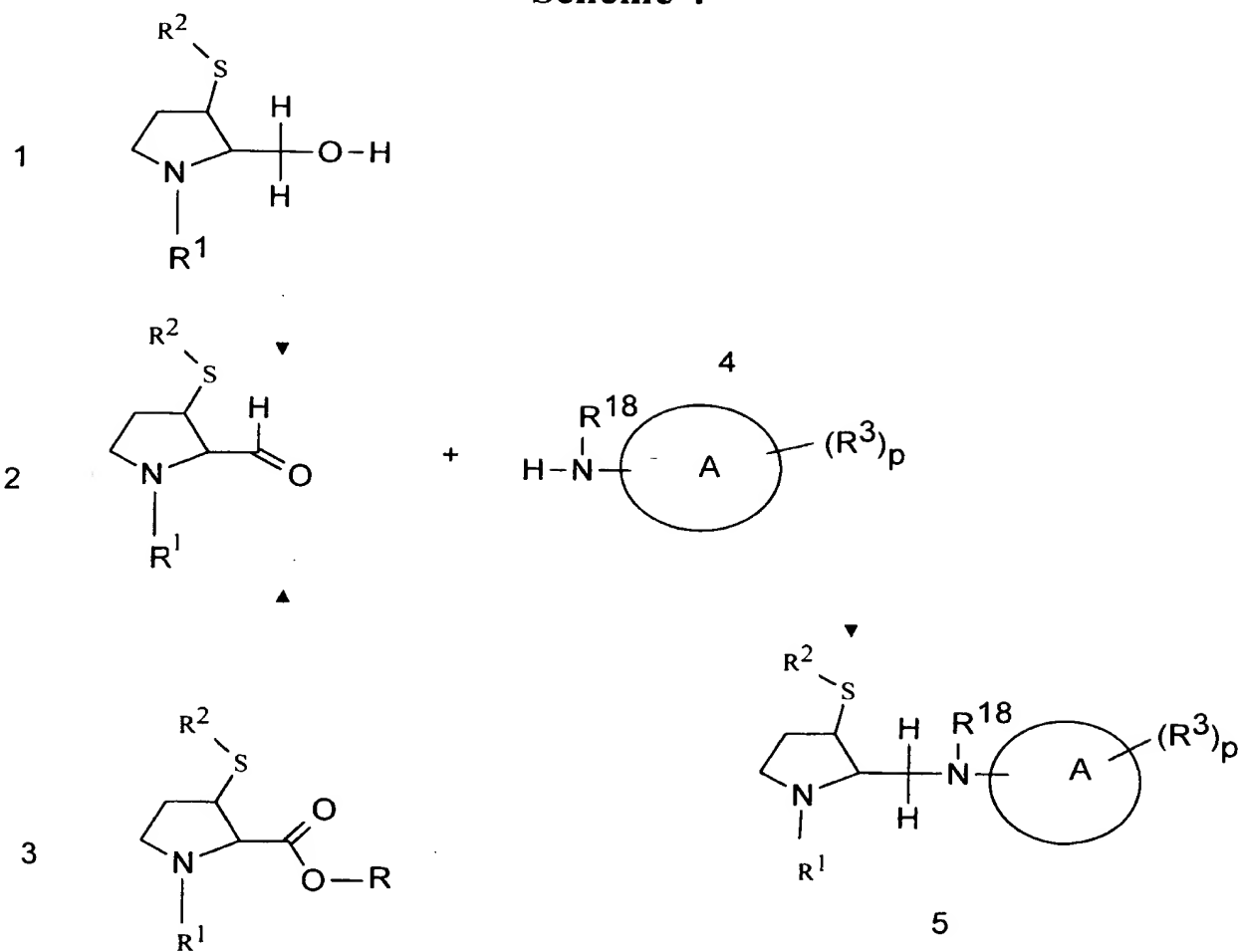
## Scheme 3





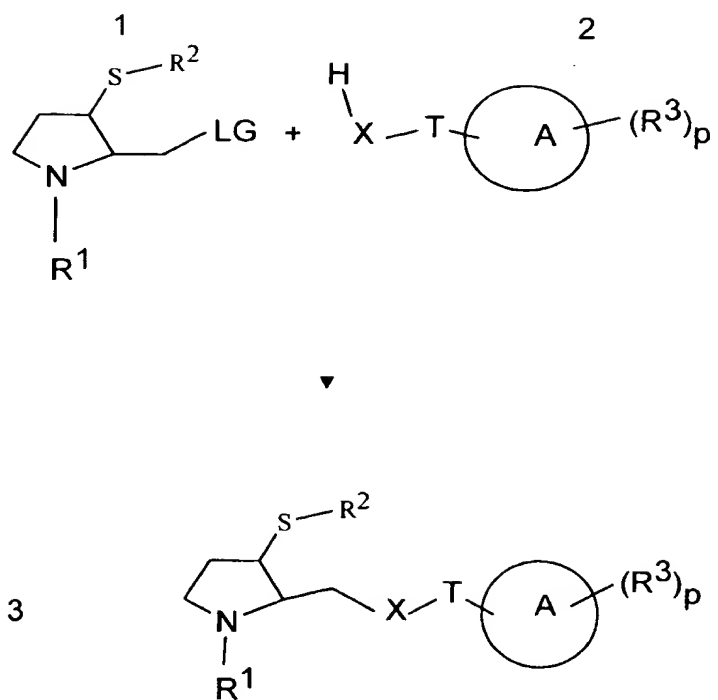


## Scheme 4





## Scheme 5





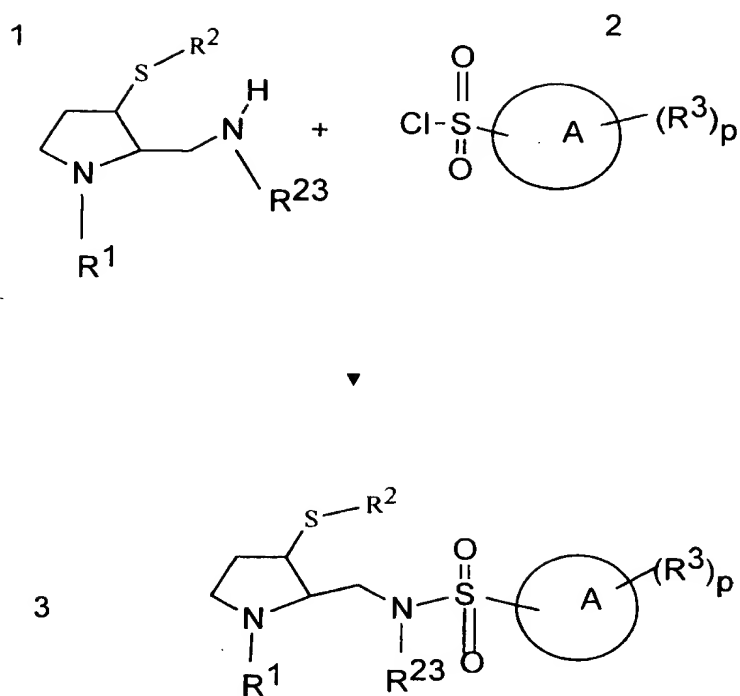
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## Scheme 6





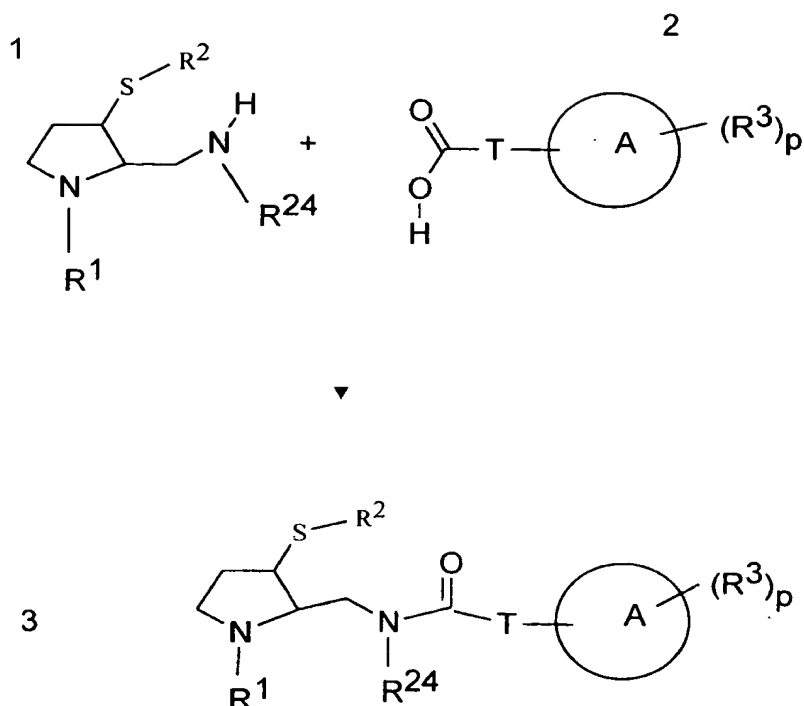
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## Scheme 7



- 5 Biological activity was tested as follows. Farnesyl protein transferase (FPT) was partially purified from human placenta by ammonium sulphate fractionation followed by a single Q-Sepharose<sup>®</sup> (Pharmacia, Inc) anion exchange chromatography essentially as described by Ray and Lopez-Belmonte (Ray K P and Lopez-Belmonte J (1992) Biochemical Society Transactions 20 494-497). The substrate for FPT was Kras (CVIM C-terminal
- 10 sequence). The cDNA for oncogenic val12 variant of human c-Ki-ras-2 4B was obtained from the plasmid pSW11-1 (ATCC). This was then subcloned into the polylinker of a suitable expression vector e.g. pIC147. The Kras was obtained after expression in the E. coli strain, BL21. The expression and purification of c-Ki-ras-2 4B and the val12 variant in E. coli has also been reported by Lowe et al (Lowe P N et al.
- 15 J. Biol. Chem. (1991) 266 1672-1678).

Incubations with enzyme contained 300nM tritiated farnesyl pyrophosphate (DuPont/New England Nuclear), 120nM ras-CVIM, 50mM Tris HCl pH 8.0, 5mM MgCl<sub>2</sub>, 10 μM ZnCl<sub>2</sub>, 5mM dithiothreitol and compounds were added at appropriate concentrations in DMSO (3% final concentration in test and vehicle control). Incubations were for 20 minutes





at 37 ° and were stopped with acid ethanol as described by Pompliano et al. (Pompliano D L et al (1992) 31 3800-3807). Precipitated protein was then collected onto glass fibre filter mats (B) using a Tomtec® cell harvester and tritiated label was measured in a Wallac®1204 Betaplate scintillation counter.

5            Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general compounds of the Formula I possess an IC<sub>50</sub> in the above test in the range, for example, 0.001 to 200µM. Thus by way of example the compound of Example 2 herein has an IC<sub>50</sub> of approximately 0.42µM.

No physiologically unacceptable toxicity was observed at the effective dose for compounds  
10 tested of the present invention.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:-

(i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;

15            (ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck,  
20 Darmstadt, Germany;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the end-products of the Formula I have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and mass spectral  
25 techniques; chemical shift values were measured on the delta scale; the following abbreviations have been used: s, singlet; d, doublet; t or tr, triplet; m, multiplet; br, broad;

(vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, infra-red (IR) or NMR analysis;

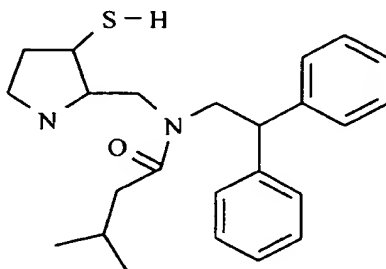
(vii) the following abbreviations have been used:-



	BOC	<u>tert</u> -butoxycarbonyl
	DCCI	1,3-dicyclohexylcarbodiimide
	DMA	<u>N,N</u> -dimethylacetamide
	DMAP	4-dimethyl-aminopyridine
5	DMF	<u>N,N</u> -dimethylformamide
	DMSO	dimethylsulfoxide
	EDC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide
	EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
	HOBt	1-hydroxybenzotriazole
10	NMM	<u>N</u> -methylmorpholine
	NMM-O	4-methylmorpholine- <u>N</u> -oxide
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	TMSI	trimethylsilyliodide
15	TPAP	tetrapropylammonium perruthenate

Note in the Schemes only those hydrogen atoms thought to assist clarity have been illustrated (ie not all hydrogen atoms have been illustrated).



Example 1**3-methyl-N-(2,2-diphenyl-ethyl)-N-(cis)-3-sulfanylpyrrolidin-2-ylmethyl)butyramide (compound 14a)**

5 1. A solution of starting material 3-methyl-N-(2,2-diphenyl-ethyl)-N-((cis)-1-BOC-3-tritylsulfanyl-pyrrolidin-2-ylmethyl)butyramide (compound 12a; 0.265g), triethylsilane (0.25 ml) in dichloromethane(2 ml) was treated with trifluoroacetic acid(16 ml) and the mixture stirred under an argon atmosphere for 30 minutes at ambient temperature and then evaporated under reduced pressure to remove most of the solvents. The residue was taken up in ethyl  
10 acetate(2 ml) and treated with 1.0M ethereal HCl. The ethyl acetate was evaporated away and diethyl ether(5 ml) and iso-hexane(20ml) were added . The gummy solid obtained gradually solidified and was isolated on a centrifuge, washed with more ether(5 ml)/iso-hexane(20 ml) and dried under high-vacuum to give the title compound as a white solid(0.125g).

NMR (CDCl<sub>3</sub>) δ: 0.80-0.95(m,6H), 1.85-2.50(m,6H), 3.00-3.15(m,1H), 3.30-3.60(m,3H),  
15 3.75-4.30(m,4H), 7.20-7.40(m,10H), 7.60(br.s,1H), 8.67(br.s,1H), 11.20(br.s,1H)

Micro Analysis

%Theory C65.2, H7.89, N6.19.

(1.0 HCl,0.5 H<sub>2</sub>O,0.14Ethyl ether)

%Found C65.2, H8.00, N6.0

The starting material was prepared as follows.

2. 3-Tritylsulfanyl-pyrrolidine-2-carboxylic acid (compound 4) was prepared from  
20 methyl 3-bromo-1-pyrrolin-2-carboxylate (compound 1) by the route described in Liebigs Ann. Chem. 1981, 1073-1088. In brief, the methyl ester of the 2-carboxylate group of compound 1 was converted to the sodium salt of the carboxylic acid using aqueous sodium hydroxide solution at 0-5°; the sodium 3-bromo dihydropyrrole was then converted to sodium 3-tritylsulfanyl-1-pyrrolin-2-carboxylate using triphenylmethylmercaptan in the presence of  
25 DME and aqueous sodium hydroxide solution at 0-5°C; then compound (4) was formed by using sodium borohydride and the pH adjusted to 5-6 with 1M HCl.



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Di-tert.-butyl dicarbonate (0.24g) was added to a stirred mixture of compound (4) (0.39g) and triethylamine(0.31 ml) in dichloromethane(3 ml) cooled to 0° C under an argon atmosphere. The mixture was allowed to warm up to ambient temperature and stirred for 60 h. It was then washed with 1.0M aqueous citric acid, brine and dried . The solvent was  
5 evaporated under reduced pressure to give 1-BOC-3-tritylsulfanyl-pyrrolidine-2-carboxylic acid (5) as a solid foam (0.446g).

3. A mixture of 1-hydroxybenzotriazole (0.142g), EDC(0.192g), 4-methylmorpholine (0.24ml) and compound 5 (0.446g) in dichloromethane (10 ml) was stirred at 5° C for 20 minutes and then for 16 h. at ambient temperature. The mixture was  
10 then washed with 1.0M aqueous citric acid and brine, dried and the solvent evaporated under reduced pressure. The product was purified by column chromatography eluting with ethyl acetate/iso-hexane(15:85) to give 1-(1-BOC-3-tritylsulfanyl-pyrrolidin-2-carbonyl)benzotriazole (compound 6) as a solid foam(0.193g).

NMR (CDCl<sub>3</sub>) δ: 1.45+1.49(s,s,9H), 2.17-2.40(m,2H), 3.08-3.27(m,2H), 3.50-3.72(m,2H),  
15 7.21-7.61(m,18H), 8.02(dd,1H)

4. A mixture of compound 6 (0.087g), N,O-dimethylhydroxylamine HCl (0.028g) and 4-dimethylaminopyridine(0.039g) in dichloromethane(2 ml) was stirred at ambient temperature for 16 h. More N,O-dimethylhydroxylamine(0.056g) and DMAP(0.078g) were added and the stirring was continued for another 16 h. The reaction was filtered and the filtrate applied  
20 directly to a chromatography column which was eluted with ethyl acetate/iso-hexane(15:85) to give (cis) 1-BOC-3-tritylsulfanyl-N-methoxy-N-methylpyrrolidine-2-carboxamide (compound 8) as a white solid (0.06g). (Note the trans stereoisomer was also formed compound 7) and isolated by column chromatography. The trans isomer was eluted from the column after the cis.

25 NMR (CDCl<sub>3</sub>) δ: 0.90-1.05(m,1H), 1.37+1.39(s,s,9H), 1.95-2.15(m,1H), 2.80-3.05(m,2H), 3.27+3.30(s,s,3H), 3.35-3.53(m,1H), 3.83+3.98(s,s,3H), 4.80-5.15(m,1H), 7.15-7.50(m,15H).

5. A solution of lithium aluminium hydride (7.0ml) in diethyl ether(1.0M ) was added dropwise over 10 minutes to a stirred solution of compound 8 (3.35 g) in THF(35 ml) cooled to -10° C under an argon atmosphere. After the addition was complete the reaction was  
30 allowed to warm to +5° C for 10 minutes and then cooled to -35° C. A solution of potassium bisulphate(1.72g in 6 ml water) was carefully added and the mixture was then allowed to





warm to ambient temperature and stirred for a further 1h. It was then filtered through diatomaceous earth (Celite™) and the filtrate diluted with diethyl ether (50 ml). The organic solution was washed with 10% aqueous citric acid, saturated aqueous sodium bicarbonate, brine, dried and the solvent removed under reduced pressure to give (cis)-1-BOC-3-

5 tritylsulfanyl-pyrrolidin-2-carbaldehyde (compound 9) as a solid foam (3.04g).

NMR (CDCl<sub>3</sub>) δ:1.32+1.37(s,s,9H), 1.65-2.05(m,2H), 3.00-3.70(m,4H), 7.20-7.53(m,15H), 9.42+9.54(s,s,1H)

6. Compound 9 (0.5 g) in dichloromethane(5 ml) was added to a stirred mixture of 2,2-diphenylethylamine(0.25 g), powdered 4 A molecular sieve(1.0 g) and sodium triacetoxy  
10 borohydride(0.27 g) in dichloromethane(20 ml) cooled to -20 °C under an argon atmosphere. The reaction mixture was then allowed to warm to ambient temperature and stirred for another 18h. The mixture was filtered through diatomaceous earth and the filtrate washed with saturated aqueous sodium bicarbonate solution and brine. The organic solution was dried and then the solvent evaporated under reduced pressure. The residue was purified by column  
15 chromatography on silica eluting with ethyl acetate/iso-hexane(20:80), followed by (30:70) to give (cis)-1-BOC-N-(2,2-diphenylethyl)-3-tritylsulfanyl-pyrrolidin-2-yl-methylamine (compound 10) as a foam(0.547 g).

NMR (CDCl<sub>3</sub>) δ:1.32+1.35(s,s,9H), 1.70-1.95(m,2H), 2.50-3.55(m,8H), 4.05-4.18(m,1H), 7.10-7.48(m,25H)

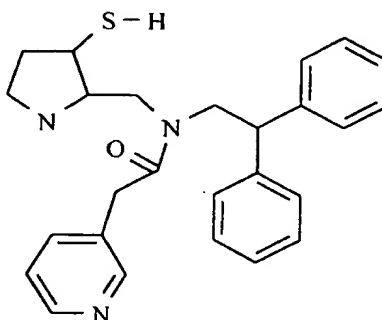
20 7. A mixture of iso-valeryl chloride (0.05 ml), compound 10 (0.25 g) and triethylamine(0.11 ml) in dichloromethane(10 ml) was stirred at ambient temperature under an argon atmosphere for 3h. The reaction was applied directly to a silica chromatography column which was eluted with ethyl acetate/iso-hexane(15:85), followed by (17:83), then (20:80) to give the desired starting material (compound 12a) as a white solid (0.292 g).

25 NMR (CDCl<sub>3</sub>) δ:0.60+0.70+0.82(d,dd,d, 6H), 1.05-1.25(m,1H), 1.30+1.33+1.36(s,s,s, 9H), 1.55-4.45(m, 13H), 7.05-7.50(m, 25H)



Example 2

**2-(3-pyridyl)-N-(2,2-diphenyl-ethyl)-N-(cis)-3-sulfanylpyrrolidin-2-ylmethyl)acetamide (compound 14(b))**



5

Compound 14(b) was prepared by a similar method to that described for preparation of compound 14(a) in Example 1.

NMR (CDCl<sub>3</sub>) δ: 2.10–2.25(m, 1H), 2.35–2.55(m, 1H), 3.15–3.53(m, 4H), 3.55–3.95(m, 3H),  
 10 4.00–4.25(m, 1H), 4.30–4.55(m, 3H), 7.10–7.50(m, 12H), 7.55–7.75(m, 1H), 8.07–8.20(m, 1H),  
 8.38–8.55(m, 1H), 8.70(s, 1H), 9.38–9.60(m, 1H), 10.25–10.43(br.s, 1H).

Micro Analysis:

%Theory C58.8, H6.45, N7.91.

(2.0 HCl, 1.5 H<sub>2</sub>O)

%Found C58.6, H6.10, N7.70

15 The starting material, 2-(3-pyridyl)-N-(2,2-diphenyl-ethyl)-N-(cis)-1-BOC-3-tritylsulfanylpyrrolidin-2-ylmethyl)acetamide (compound 12(b)), was prepared as follows:

A mixture of HOBT(0.076g), EDC(0.103g), 4-methylmorpholine(0.23 ml) and compound 10 (see Example 1; 0.269 g) and 3-pyridylacetic acid (0.093g) in dichloromethane(12 ml) was stirred at 5° C for 15 minutes and then at ambient temperature  
 20 for 20h. The solution was then applied to a silica chromatography column which was eluted with ethyl acetate/iso-hexane(30:70), followed by (60:40), then (90:10) and ethyl acetate to give the compound 12b as a white solid (0.217 g).

NMR (CDCl<sub>3</sub>) δ1.05–1.25(m, 1H), 1.37(s, 9H), 1.70–4.50(m, 12H), 7.05–7.55(m, 27H), 7.78–8.50(m, 2H)

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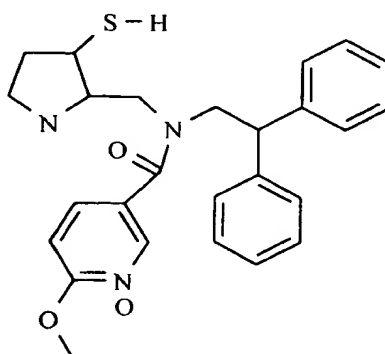
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Example 3

**6-Methoxy-1-oxido-N-(2,2-diphenylethyl)-N-((cis)-3-sulfanylpyrrolidin-2-ylmethyl)-pyridine-3-carboxamide (compound 14(c))**

5



Compound 14(c) was prepared by a similar method to that described for the preparation of compound 14a in Example 1.

NMR (CDCl<sub>3</sub>) δ 1.15-1.35(m,1H), 1.88-2.03(m,1H), 2.21(d,1H), 2.28-2.50(m,1H), 3.00-3.20(m,1H), 3.20-3.37(m,1H), 3.42-3.55(m,1H), 3.69(d,1H), 3.80-3.98(m,1H), 4.05(s,3H), 4.20-4.40(m,3H), 6.58(d,1H), 7.08-7.36(m,11H), 8.11(s,1H), 9.10(br.s,1H), 10.8(br.s,1H)

Micro Analysis: %Theory C60.0, H6.59, N8.08.

(1.0 HCl, 1.0 H<sub>2</sub>O) %Found C59.6, H6.00, N7.80

The starting material, 6-methoxy-1-oxido-N-(2,2-diphenyl-ethyl)-N-((cis)-1-BOC-3-tritylsulfanylpyrrolidin-2-ylmethyl)pyridine-3-carboxamide (compound 12(c)), was prepared from compound 10 (see Example 1) using the method described for compound 12(b) (in Example 2) using appropriate intermediates.

NMR (CDCl<sub>3</sub>) δ: 0.75-1.00(m,1H), 1.10-1.25(m,1H), 1.25-1.45(m,9H), 1.90-3.75(m,8H), 3.90-4.15(m,3H), 4.20-4.90(m,1H), 6.30-6.55(m,1H), 6.60-7.50(m,27H)

20

Example 4

a) **N-(naphth-1-yl-ethyl)-N-((cis)-3-sulfanylpyrrolidin-2-yl-methyl)-thiazole-5-carboxamide (compound 15(a)); and**

b) **6-Methoxy-1-oxido-N-(naphth-1-yl-ethyl)-N-((cis)-3-sulfanylpyrrolidin-2-ylmethyl)pyridine-3-carboxamide (compound 15(b))**

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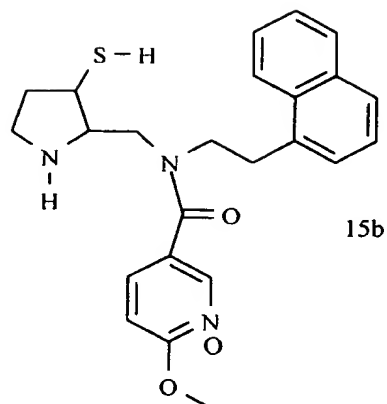
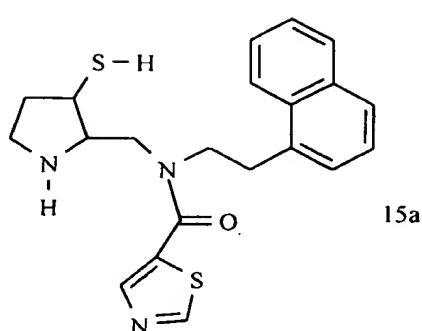


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Compound 15(a) and compound 15(b) were prepared by similar methods to those described for preparation of compound 14(a) in Example 1. The starting materials for compounds 15(a) and 15(b) were prepared from compound 9 (Example 1) using appropriate intermediates by similar procedures to those described in the synthesis of compounds 12(b) and 12(c) in Examples 2 and 3. In brief, the following reagents were used with respect to the steps numbered in Example 1.

10 Step 6: 1-naphthylamine/ sodium triacetoxyborohydride/ molecular sieve/  $-20^{\circ}$

Step 7: thiazole-5-carboxylic acid (for 15(a)) or 6-methoxynicotinic acid N-oxide (for 15(b))/ EDC/ HOBt/ 4-methylmorpholine.

Characterising data:

Compound 15(a):

15 NMR (DMSO- $d_6$ )  $\delta$ : 1.90-2.05(m,1H), 3.10-4.10(m,11H), 7.30-7.95(m,8H), 8.12(s,1H), 9.08(s,1H), 9.30(br.s,1H), 10.05(br.s,1H)

Micro Analysis: %Theory C52.6, H5.47, N8.76

(2.0 HCl,0.5 H<sub>2</sub>O) %Found C52.7, H5.3, N8.5

Compound 15b:

20 NMR (CDCl<sub>3</sub>)  $\delta$ :2.30-2.45(m,2H), 2.90-4.15(m,13H), 6.27(d,1H), 6.90-8.05(m,10H), 9.20(br.s,1H), 10.60(br.s,1H)

Micro Analysis: %Theory C57.7, H6.36, N8.24

(1.0HCl,1.5 H<sub>2</sub>O,0.12Ethyl ether) %Found C57.8, H6.0, N8.2





(cis)-1-BOC-N-(naphth-1-ethyl)-3-tritylsulfanyl-pyrrolidin-2-yl-methylamine which is the product (compound 11) of the reaction equivalent to step 6 (Example 1):

NMR (CDCl<sub>3</sub>) δ 0.80-0.95(m, 1H), 1.34(s, 9H), 1.70-2.00(m, 1H), 2.50-3.65(m, 10H), 7.15-7.50(m, 19H), 7.65-7.73(m, 1H), 7.80-7.88(m, 1H), 8.00-8.12(m, 1H).

5 N-(naphth-1-yl-ethyl)-N-((cis)-1-BOC-3-tritylsulfanylpyrrolidin-2-yl-methyl)-thiazole-5-carboxamide (compound 13(a)) which is the product of the reaction equivalent to step 7 of Example 1 for synthesis of compound 15(a).

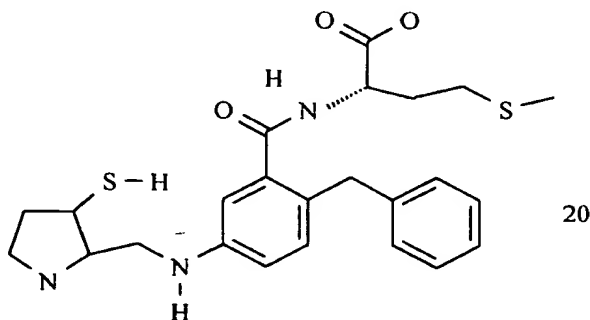
NMR (CDCl<sub>3</sub>) δ: 0.80-0.95(m, 1H), 1.28(s, 9H), 1.80-4.40(m, 11H), 7.10-8.80(m, 24H).

6-Methoxy-1-oxido-N-(naphthyl-1-yl-ethyl)-N-((cis)-1-BOC-3-tritylsulfanylpyrrolidin-2-ylmethyl)pyridine-3-carboxamide (compound 13(b)) which is the product of the reaction equivalent to step 7 (Example 1) for compound 15(b):

NMR (CDCl<sub>3</sub>) δ: 0.80-0.95(m, 1H), 1.30(s, 9H), 1.90-4.20(m, 14H), 5.95-6.10(m, 1H), 6.70-7.85(m, 24H).

#### 15 Example 5

**(2S)-2-{2-Benzyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]benzoylamino}-4-methylsulfanylbutyric acid**



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Compound 20 was prepared from compound 19 by standard procedures. In brief, 2N aqueous sodium hydroxide solution was added to a stirred solution of compound 19 in methanol at room temperature under argon. After 18 h the reaction mixture was concentrated to remove the Methanol. The resulting residues were dissolved in distilled water (2.0 mL) and acidified to pH3 with 2N HCl. The resulting solution was purified by reverse phase HPLC (Dynamax

25



C18,8 $\mu$  precolumn), eluting with a gradient of 0-40% Methanol/distilled water. Product fractions were concentrated and the desired end product purified by standard methods.

$^1\text{H}$ NMR (DMSO- $d_6$  +  $\text{CD}_3\text{COOD}$ )  $\delta$ : 1.96(5H,m), 2.5(5H,m+DMSO), 3.18-3.48(3.5H,m), 3.75-4.04 (3.5H,m), 4.46(1H,q), 6.61(2H,m,Ar), 6.94-7.23(6H,m,Ar).

5 MS (ESP+)  $m/z$  (M+H) $^+$  474.

Anal. Calcd for  $\text{C}_{24}\text{H}_{31}\text{N}_3\text{S}_2\text{O}_3 \cdot 1.6\text{TFA}$  C, 49.8; H, 5.01; N, 6.4; Found C, 49.5; H, 5.1; N, 6.4

The starting material was prepared as follows:

Isopropyl (2S)-2-{2-Benzyl-5-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl-  
10 amino]benzoylamino}-4-methylsulfanylbutyrate (compound 19) was prepared from compound 18 using a similar procedure to that of Example 1, step 1

Isopropyl (2S)-2-{2-benzyl-5-[(cis)-3-tritylsulfanylpyrrolidin-2-  
ylmethylamino]benzoylamino}-4-methylsulfanylbutyrate (compound 18) was prepared by  
15 reacting compound 9 (Example 1) with isopropyl (2S)-2-(5-amino-2-benzylbenzoylamino)-4-methylsulfanylbutyrate (compound 17) according to standard procedures. In brief, a solution containing compounds 9 and 17 in isopropyl alcohol was treated with powdered 4 $\text{\AA}$  molecular sieves and the resulting suspension was stirred at room temperature for 1h. Acetic acid and sodium cyanoborohydride were then added and the reaction mixture was left to stir for 18h at room temperature. The reaction mixture was then partitioned between ethyl acetate(50mL)  
20 and saturated sodium hydrogen sulphate(aq) (50mL). The aqueous phase was then washed with ethyl acetate (50mL) and the combined organics dried over  $\text{MgSO}_4$ , filtered and concentrated to a colourless gum. This was then purified by flash chromatography on Silica (Varian Mega Bond Elut Column) eluting a gradient of 25-40% Ethyl acetate/i-hexane to give compound 18.

25 Compound 17 was prepared as follows:

A solution of methyl (2S)-2-(2-benzyl-5-nitro-benzoylamino)-4-methylsulfanyl-butyrate compound 34(d) (25.24g, 62.78mmol) in methanol (500mL) was treated with 2N aqueous sodium hydroxide solution (35mL, 70mmol). The resulting solution was then evaporated to dryness and the solids partitioned between ethyl ether (200mL) and water (500mL). The  
30 aqueous material was then acidified to pH2 with 2N HCl and extracted with ethyl acetate (2x250mL). The combined organics were washed with water(2x100mL), brine(100mL),



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filtered through phase separating paper and evaporated to give (2S)-2-(2-benzyl-5-nitro-benzoylamino)-4-methylsulfanyl-butyric acid (compound 36(a)) as a white solid, 23.57g (96.8%).

$^1\text{H}$  NMR (DMSO- $d_6$ , 300MHz)  $\delta$ : 1.8-2.2(5H, m); 2.3-2.6(2H+DMSO, m);  
5 4.1-4.3(2H, m); 4.4-4.6(1H, m); 7.1-7.3(5H, m); 7.4-7.6(1H, m); 8.1-8.3(2H, m);  
8.9-9.0(1H, m, NHCO)

MS (ESP-) m/z 387(M-H).

Sulphuryl chloride (5.0mL, 62mmol) was added to a stirred suspension of compound 36a (19.2g, 50mmol) in IPA (500mL). The resulting mixture was then heated at reflux for  
10 18hrs. The reaction mixture was then evaporated to 1/5 volume and partitioned between ethyl acetate (1L) and saturated aqueous sodium hydrogen sulphate (500mL). The organics were then washed with water (200mL), brine (200mL), filtered through phase separating paper and evaporated to give isopropyl (2S)-2-(2-benzyl-5-nitro-benzoylamino)-4-methylsulfanyl-butyrates (compound 36(b)) as a white solid, 21.25g (100%).

15  $^1\text{H}$  NMR (DMSO- $d_6$ , 300MHz)  $\delta$ : 1.0-1.3(6H, m); 1.8-2.2(5H, m);  
2.3-2.6(2H+DMSO, m); 4.1-4.3(2H, m); 4.4-4.6(1H, m); 4.8-5.0(1H, m); 7.1-7.3(5H, m);  
7.4-7.6(1H, m); 8.1-8.3(2H, m); 9.0(1H, m, NHCO)

MS (ESP+) m/z 431(M+H)+.

$\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  (2.5g, 11.08mmol) was added to a stirred solution of compound 36(b)  
20 (2.24mmol) in ethyl acetate (50mL) and the resulting mixture heated at reflux for 18hrs. The reaction mixture was cooled to ambient temperature and treated with 0.880 SG  $\text{NH}_3$ (aq) dropwise to pH8. The resulting precipitate was removed by filtration through diatomaceous earth. The filtrates were then evaporated and purified by chromatography (Mega Bond Elut, Silica), eluting with dichloromethane and then 50% ethyl acetate/ i-hexane to give the  
25 desired aniline compound (17).



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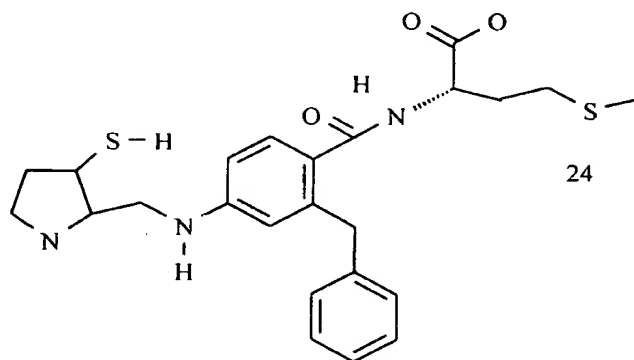
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Example 6**(2S)-2-{2-Benzyl-4-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethylamino]benzoylamino}-4-methylsulfanylbutyric acid**

Compound 24 was prepared from compound 9 (Example 1) and methyl (2S)-2-(4-amino-2-benzyl-benzoylamino)-4-methylsulfanyl-butyrates (compound 21) according to procedures outlined in Example 5.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub> + CD<sub>3</sub>COOD) δ: 1.98(5H,m), 2.48(5H,m), 3.18-3.46(3.5H,m), 3.75(1H,m), 3.9-4.2(2.5H,m), 4.43(1H,m), 6.46(2H,m,Ar), 7.04-7.34(6H,m,).

MS (ESP+) m/z (M+H)<sup>+</sup> 474.

Microanalysis, calculated for C<sub>24</sub>H<sub>31</sub>N<sub>3</sub>S<sub>2</sub>O<sub>3</sub>·1.55TFA: C, 50.0; H, 5.04; N, 6.46; Found C, 49.9; H, 5.1; N, 6.4.

Compound 21 used in the preparation of compound 24 was prepared as follows.

Sodium dichromate dihydrate (151gm) was added to glacial acetic acid (575 ml) followed by 2-bromo-4-nitro-toluene (49.7gm). To this solution was added dropwise sulphuric acid (175ml) at such a rate to maintain the temperature between 75-85°C. This mixture was heated to 100-110°C for 3h cooled to 50°C and poured onto ice (1litre). The aqueous phase was

extracted with ethyl acetate, the organic layer back extracted with Aqueous sodium hydroxide solution and the resulting basic aqueous layer acidified with concentrated hydrochloric acid. The precipitated solid was filtered, washed with water and air dried to give 15.72 gm (28%) of 2-bromo-4-nitro-benzoic acid (compound 26) as a white solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 7.42 (1H,d), 8.08 (1H,q), 8.42 (1H,d)





Compound 26 in methanol was treated with  $\text{SO}_2\text{Cl}_2$  and the resulting solution heated at reflux for 18h. The reaction mixture was then evaporated, pre-absorbed on silica (Merck, 9385) and purified by chromatography, eluting with 10% ethyl acetate/i-hexane.

Appropriate fractions were combined and evaporated to give methyl 2-bromo-4-nitro-5 benzoate (compound 27).

A solution of benzyl bromide (2.0mL, 17.3mmol) in THF (10mL) was added dropwise at  $0^\circ\text{C}$  to a stirred suspension of zinc dust (1.7g, 26mmol) in THF (10mL) which had been activated according to the method described by Knochel (J.O.C. 53, 2392, 1988). The mixture was left to warm to ambient temperature and stir for 3h. An aliquot (6.5mmol) of the supernatant containing the benzyl zinc reagent was then added to a stirred solution of compound 27 (3.85mmol) and  $\text{Pd}(\text{dba})_3$  (0.0385mmol) in THF (10mL) at ambient temperature under argon. After 1hr a second aliquot (6.5mmol) of the benzyl zinc reagent was added. The resulting black reaction mixture was quenched with 2N HCl (250mL) and extracted with Ethyl acetate (2x100mL). The combined organics were washed with water (50mL) and brine (50mL), filtered through phase separating paper and evaporated to an orange gum. This was purified by chromatography on silica (Merck, 9385) eluting with 10% ethyl acetate/i-hexane to give methyl 2-benzyl-4-nitro-benzoic acid (compound 28).

2N Aqueous sodium hydroxide solution (2.0mL, 4mmol) was added to a solution of compound (28) (2.06mmol) in methanol (10mL) at ambient temperature. After 2hrs the reaction mixture was evaporated to remove the methanol and then partitioned between ethyl ether (20mL) and 2N aqueous sodium hydroxide solution (20mL). The aqueous phase was acidified to pH 2/3 with 2N HCl and extracted with ethyl acetate (3x20mL). The combined organics were washed with water (20mL) and brine (20mL), filtered through phase separating paper and evaporated to yield 2-benzyl-4-nitro-benzoic acid (compound 29).

Compound 29 (2.45mmol) was coupled with L-methionine methyl ester hydrochloride (540mg, 2.7mmol) to give methyl 2-[(2-benzyl-4-nitro-benzoyl)amino]-4-methylsulfanylbutyrate (compound 30).

$\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  (2.5g, 11.08mmol) was added to a stirred solution of compound 30 (2.24mmol) in ethyl acetate (50mL) and the resulting mixture heated at reflux for 18h. The reaction mixture was cooled to ambient temperature and treated with 0.880 SG  $\text{NH}_3(\text{aq})$  dropwise to pH 8. The resulting precipitate was removed by filtration through diatomaceous



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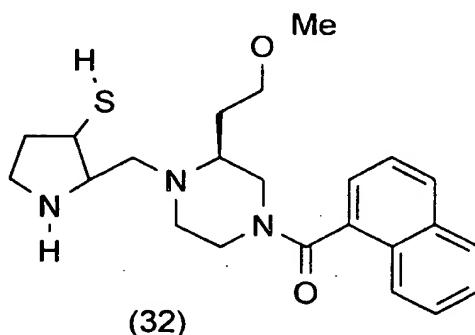
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earth (Celite®)(545). The filtrates were then evaporated and purified by chromatography (Mega Bond Elut, Silica), eluting with dichloromethane and then 50% ethyl acetate/ i-hexane to give the desired compound 21.

### 5 Example 7

#### **(2S)-2-(2-methoxy-ethyl)-1-((cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-4-naphthoyl-piperazine**



Compound 32 was synthesised from starting material (2S)-2-(2-methoxy-ethyl)-1-  
 10 [cis]-1-BOC-3-tritylsulfanyl-pyrrolidin-2-ylmethyl)-4-naphthoyl-piperazine (compound 31)  
 using a similar method to that of Example 1, step 1.

NMR (CDCl<sub>3</sub>) δ 1.70–4.90(m, 24H), 7.35-8.00(m, 7H), 9.40-10.30(br.s, 1H), 10.50-  
 11.80(br.s, 1H).

Micro Analysis: %Theory C54.0, H7.20, N8.01

15 (2.0HCl, 1.5H<sub>2</sub>O, 0.15 ethyl ether) %Found C54.3, H7.00, N8.00

The starting material was prepared as follows. Compound 31 was synthesised from  
 compound 9 (see Example 1) and (3S)-3-(2-methoxy-ethyl)-1-naphthoyl-piperazine  
 (compound 16) by the method described in Example 1, step 6, for the preparation of  
 compound 10. Compound 16 was prepared using analogous methods to those described in  
 20 International Patent Application WO 95/00497 (Merck; Graham et al); see compound VIII,  
 Scheme 2 and Example 7, Step E therein substituting naphthoic acid in lieu of 2,3-  
 dimethylbenzoic acid.

NMR, compound 31, (CDCl<sub>3</sub>) δ: 0.80-1.20(m, 1H), 1.30-1.43(m, 9H), 1.75-3.75(m, 20H),  
 3.95-4.55(m, 1H), 7.15-7.95(m, 22H).



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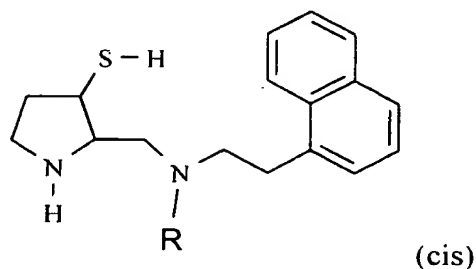
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Example 8

The compounds in the following table were prepared from the appropriate tritylsulfanyl compounds using a similar method to that described in Example 1, paragraph 1.

5



Compound No.

R

10

15c

isovaleryl

15d

3-pyridylacetyl

15e

1-oxido-6-methoxypyridin-3-ylcarbonyl

15f

thiazol-5-ylcarbonyl

15

Characterising data:

Compound 15(c):

NMR (CDCl<sub>3</sub>)  $\delta$ : 0.75(t, 6H), 1.15-1.38(m, 1H), 1.50-1.80(m, 3H), 1.90-2.15(m, 1H), 2.32-2.52(m, 1H), 2.75-2.97(m, 1H), 3.00-3.26(m, 1H), 3.26-4.00(m, 8H), 7.25-8.03(m, 7H), 8.80-9.20(br.s, 1H), 11.2-11.7(br.s, 1H).

20

Micro Analysis:

%Theory C64.90, H7.68, N6.88, S7.88

(1.0 HCl)

%Found C65.20, H7.50, N6.90, S7.90

Compound 15(d):

NMR (DMSO-d<sub>6</sub>)  $\delta$ : 1.75-2.00(m, 1H), 2.30-2.60(m, 1H), 2.90-4.50(m, 12H), 7.40-7.65(m, 4H), 7.75-8.00(m, 3H), 8.15-8.30(m, 2H), 8.65-8.90(m, 3H), 9.90-10.40(m, 1H).

25

Micro Analysis:

%Theory C56.00, H6.46, N8.17, S6.23



(2.0 HCl, 2.0H<sub>2</sub>O) %Found C55.70, H6.30, N8.20, S6.00

Compound 15(e):

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.10-1.40(m, 1H), 1.80-2.12(m, 2H), 2.40-2.60(m, 1H), 2.96-3.20(m, 1H),  
3.20-3.45(m, 4H), 3.55-3.72(m, 1H), 3.78-4.07(m, 4H), 4.13-4.30(m, 1H), 6.25(d, 1H),

5 6.92(d, 1H), 7.15-7.89(m, 8H), 8.92-9.20(br.s, 1H), 10.6-10.8(br.s, 1H).

Micro Analysis: %Theory C58.20, H6.18, N8.48, S6.47

(1.0HCl, 1.20H<sub>2</sub>O) %Found C57.80, H5.80, N8.50, S6.50

Compound 15(f):

NMR (DMSO-d<sub>6</sub>)  $\delta$ : 1.80-2.00(m, 1H), 2.35-2.55(m, 1H), 3.05-4.05(m, 10H), 7.28-7.54(m,  
10 5H), 7.74-7.94(m, 3H), 8.13(s, 1H), 9.10(s, 2H), 9.80-10.00(br.s, 1H).

Micro Analysis: %Theory C53.60, H5.36, N8.93, S13.60

(2.0 HCl) %Found C54.00, H5.50, N9.00, S13.30

The starting materials were prepared as follows:

15 Compound 13(c) was prepared from compound 7 via trans-1-BOC-3-tritylsulfanylpyrrolidin-2-carbaldehyde (compound 9(a)) and trans-N-(naphth-1-ylethyl)-1-BOC-3-tritylsulfanylpyrrolidin-2-ylmethanamide and (compound 11(a)) using a similar method to that described for the preparation of compound 12(a) but using 1-naphthylethylamine instead of 2,2-diphenylethylamine in paragraph 6.

20 Characterising data:

Compound 7:

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.05-1.35(m, 1H), 1.42+1.44(s,s, 9H), 1.50-1.70(m, 1H), 2.77-2.94(m, 1H), 3.17+3.18(s,s, 3H), 3.30-3.56(m, 2H), 3.73+3.85(s,s, 3H), 4.60-4.95(m, 1H), 7.15-7.55(m, 15H).

25 Compound 9(a):

NMR (CDCl<sub>3</sub>)  $\delta$  1.33+1.37(s,s, 9H), 1.60-2.08(m, 2H), 3.00-3.20(m, 2H), 3.35-3.68(m, 2H), 7.20-7.55(m, 15H), 9.42+9.54(s,s, 1H).

Compound 11(a):

NMR (CDCl<sub>3</sub>)  $\delta$  1.15-1.30(m, 1H), 1.43(s, 9H), 1.65-1.80(m, 1h), 2.40-2.57(m, 1H), 2.83-  
30 2.92(m, 3H), 3.05-3.20(m, 3H), 3.35-3.95(m, 3H), 7.13-8.05(m, 22H).





Compound 13(c):

NMR (CDCl<sub>3</sub>)  $\delta$  0.60-1.00(m, 6H), 1.15-1.35(m, 1H), 1.40-1.47(m, 9H), 1.50-2.30(m, 4H), 2.45-4.15(m, 10H), 7.10-8.30(m, 22H).

Compounds 13(d) to 13(f) were prepared from compound 11(a) by the method described in the preparation of compound 15(a) (Example 4) using the appropriate "acid".

Characterising data:

Compound 13(d):

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.15-1.33(m, 1H), 1.40-1.53(m, 9H), 1.85-2.15(m, 1H), 2.50-4.25(m, 12H), 6.85-8.55(m, 26H).

10 Compound 13(e):

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.10-1.30(m, 1H), 1.43(s, 9H), 1.60-4.10(m, 14H), 6.00-6.40(m, 1H), 6.60-6.75(m, 1H), 6.90-7.90(m, 23H)

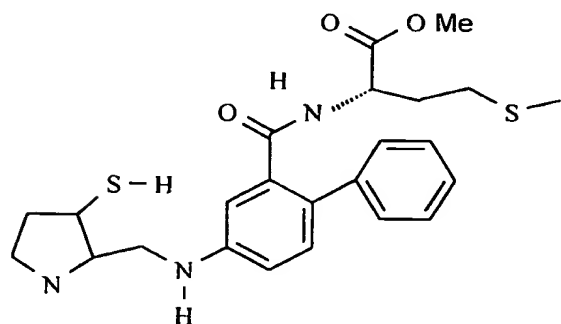
Compound 13(f):

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.05-1.30(m, 1H), 1.43(s, 9H), 1.70-4.20(m, 11H), 7.10-7.90(m, 23H),  
15 8.57-8.80(m, 1H).

### Example 9

**Methyl (2S)-2-[2-phenyl-5-(trans-3-sulfanylpyrrolidin-2-ylmethylamino)benzoylamino]-4-methylsulfanylbutyrate (compound 37)**

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Methyl (2S)-2-[2-phenyl-5-(trans-3-sulfanylpyrrolidin-2-ylmethylamino)benzoylamino]-4-methylsulfanylbutyrate (compound 37) was prepared from methyl (2S)-2-[2-phenyl-5-(trans-3-tritylsulfanylpyrrolidin-2-ylmethylamino)benzoylamino]-4-methylsulfanylbutyrate

25 (compound 33) by a similar method to that described in Example 1, step 1.



Compound 37:

NMR (DMSO- $d_6$ )  $\delta$ : 1.76-1.94(m, 3H), 1.97(s, 3H), 2.10-2.30(m, 2H), 2.35-2.50(m, 1H), 3.13-3.58(m, 7H), 3.61(s, 3H), 4.30-4.39(m, 1H), 6.70(d, 1H), 6.79(dd, 1H), 7.15-7.30(m, 6H), 8.53(d, 1H), 9.42(br.s, 1H), 9.84(br.s, 1H).

5

Micro Analysis :	% Theory C51.70, H6.18, N7.54, S11.50
(2.0 HCl, 0.6H <sub>2</sub> O)	% Found C51.80, H5.90, N7.90, S11.60

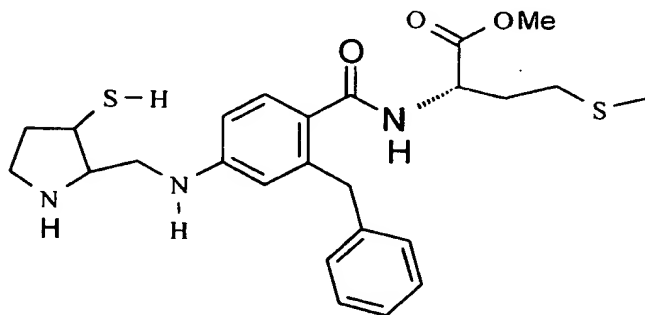
Compound 33 was prepared from compound 9(a) following the procedure described in the preparation of compound 18 (from Example 5) using the appropriate "aniline", methanol as solvent and employing 3Å powdered sieves.

Compound 33:

NMR (DMSO- $d_6$ )  $\delta$  : 0.80-0.95(m, 1H), 1.38-1.45(m, 9H), 1.70-1.92(m, 3H), 1.97(s, 3H), 2.10-2.30(m, 2H), 2.70-2.86(m, 1H), 2.95-3.22(m, 4H), 3.60-3.65(m, 3H), 3.87-3.95(m, 1H), 4.30-4.43(m, 1H), 6.02(br.s, 1H), 6.60-6.78(m, 2H), 7.05-7.37(m, 21H), 8.30-8.50(m, 1H).

#### Example 10

**Methyl (2S)-2-[2-benzyl-4-((trans)-3-sulfanylpyrrolidin-2-ylmethylamino)benzoylamino]-4-methylsulfanylbutyrate (compound 38)**



20

Methyl (2S)-2-[2-benzyl-4-((trans)-3-sulfanylpyrrolidin-2-ylmethylamino)benzoylamino]-4-methylsulfanylbutyrate (compound 38) was prepared from methyl (2S)-2-[2-benzyl-4-(trans-1-tert-butoxycarbonyl-3-tritylsulfanylpyrrolidin-2-ylmethylamino)benzoylamino]-4-methylsulfanylbutyrate using a similar method to that described in Example 1, step 1.

25



Compound 38:

NMR (DMSO- $d_6$ )  $\delta$ : 1.76-2.01(m, 3H), 2.03(s, 3H), 2.30-2.50(m, 2H), 3.10-3.55(m, 7H), 3.61(s, 3H), 3.99-4.17(m, 2H), 4.43-4.53(m, 1H), 6.49-6.54(m, 2H), 7.05-7.30(m, 6H), 8.39(d, 1H), 9.35(br.s, 1H), 9.79(br.s, 1H).

Micro Analysis :                      %Theory C53.60, H6.29, N7.50, S11.44  
(2.0 HCl)                              % Found C53.40, H6.70, N7.60, S11.40

Compound 34 was prepared from compound 9(a) and the appropriate aniline using a similar method to that used to prepare compound 18 in Example 5.

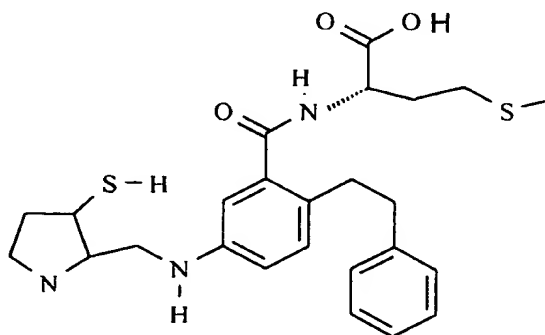
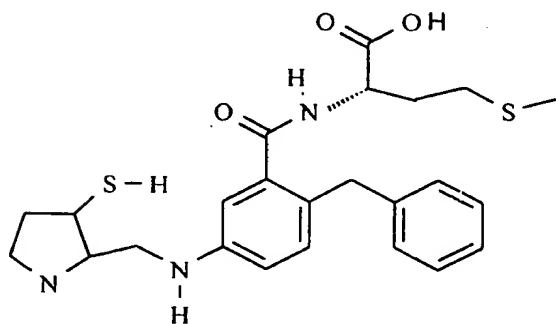
Compound 34:

NMR (DMSO- $d_6$ )  $\delta$  : 0.73-0.90(m, 1H), 1.39-1.45(m, 9H), 1.62-1.75(m, 1H), 1.93-2.04(m, 2H), 2.05(s, 3H), 2.63-2.78(m, 1H), 2.88-3.30(m, 5H), 3.63(s, 3H), 3.85-4.27(m, 4H), 4.47-4.57(m, 1H), 6.00-6.09(br.s, 1H), 6.30-6.60(m, 2H), 7.08-7.32(m, 21H), 8.33-8.40(m, 1H).

#### Example 11

(2S)-2-[2-Benzyl-5-((trans)-3-sulfanylpyrrolidin-2-ylmethylamino)benzoylamino]-4-methylsulfanylbutyric acid (compound 41) and (2S)-2-[2-phenethyl-5-((trans)-3-sulfanylpyrrolidin-2-ylmethylamino)benzoylamino]-4-methylsulfanylbutyric acid

(compound 42)



(2S)-2-[2-Benzyl-5-((trans)-3-sulfanylpyrrolidin-2-ylmethylamino)benzoylamino]-4-methylsulfanylbutyric acid (compound 41) and (2S)-2-[2-phenethyl-5-((trans)-3-sulfanylpyrrolidin-2-ylmethylamino)benzoylamino]-4-methylsulfanylbutyric acid (compound



42) were prepared from the appropriate methyl ester (compounds 39 and 40 respectively) using a similar method to that used to prepare compound 27 (Example 6).

Compound 41:

5 NMR (DMSO- $d_6$ )  $\delta$  : 1.80-2.02(m, 3H), 2.02(s, 3H), 2.25-2.42(m, 2H), 3.10-3.75(m, 7H), 3.82-4.02(m, 2H), 4.39-4.47(m, 1H), 6.60-6.68(m, 2H), 6.95(d, 1H), 7.05-7.22(m, 5H), 8.48-8.55(m, 1H), 9.60(br.s, 1H), 9.93(br.s, 1H).

Micro Analysis:	%Theory C47.60, H5.50, N6.95
(2.00HCl, 1.00NaCl)	%Found C47.3, H5.10, N6.70

10 Compound 42:

NMR (DMSO- $d_6$ )  $\delta$  : 1.75-2.00(m, 3H), 2.00(s, 3H), 2.30-2.90(m, 6H), 3.05-3.57(m, 7H), 4.43-4.53(m, 1H), 6.62-6.70(m, 2H), 7.00(d, 1H), 7.10-7.27(m, 5H), 8.50(d, 1H), 9.35(br.s, 1H), 9.78(br.s, 1H)

Micro Analysis:	%Theory C52.20, H6.13, N7.31
15 (2.00HCl, 0.25NaCl)	%Found C52.20, H6.00, N7.10

Compounds 39 and 40 were prepared from compound 9(a) via the trityl-protected sulfanyl compounds (compound 35 and 36 respectively) using a similar method to that used to prepare compound 37 (Example 10).

20 Compound 35:

NMR (DMSO- $d_6$ )  $\delta$  0.85-0.97(m, 1H), 1.35-1.45(m, 9H), 1.67-1.83(m, 1H), 1.90-2.05(m, 2H), 2.03(s, 3H), 2.64-2.80(m, 1H), 2.92-3.32(m, 5H), 3.63(s, 3H), 3.82-4.05(m, 4H), 4.45-4.57(m, 1H), 5.63-5.75(br.s, 1H), 6.50-6.62(m, 2H), 6.83-6.93(m, 1H), 7.07-7.33(m, 20H), 8.53-8.59(m, 1H).

25 Compound 39:

NMR (DMSO- $d_6$ )  $\delta$  1.75-2.03(m, 3H), 2.03(s, 3H), 2.30-2.50(m, 2H), 3.07-3.58(m, 7H), 3.60(s, 3H), 3.83-4.00(m, 2H), 4.42-4.58(m, 1H), 6.60-6.70(m, 2H), 6.90-7.24(m, 6H), 8.60-8.70(m, 1H), 9.35(br.s, 1H), 9.75(br.s, 1H).

Micro Analysis:	%Theory C52.30, H6.41, N7.32, S11.17
30 (2.00HCl, 0.75H <sub>2</sub> O)	%Found C52.40, H6.40, N7.50, S11.10





## Compound 36:

NMR (DMSO-d<sub>6</sub>)  $\delta$  : 0.83-0.93(m, 1H), 1.38-1.45(m, 9H), 1.68-1.85(m, 1H), 1.97-2.07(m, 5H), 2.50-3.23(m, 11H), 3.61(s, 3H), 3.83-4.03(m, 1H), 4.53-4.61(m, 1H), 5.67(br.s, 1H), 6.50-6.63(m, 2H), 6.90-6.99(m, 1H), 7.10-7.35(m, 20H), 8.55-8.60(m, 1H)

## 5 Compound 40:

NMR (DMSO-d<sub>6</sub>)  $\delta$  : 1.75-2.06(m, 3H), 2.03(s, 3H), 2.34-2.92(m, 6H), 3.10-3.57(m, 7H), 3.60(s, 3H), 4.50-4.60(m, 1H), 6.63-6.70(m, 2H), 7.00-7.28(m, 6H), 8.68(d, 1H), 9.38(br.s, 1H), 9.80(br.s, 1H).

## Micro Analysis:

%Theory C53.5, H6.56, N7.20, S10.99

10 (2.00HCl, 0.50 H<sub>2</sub>O)

%Found C53.5, H6.30, N7.20, S10.90

Methyl (2S)-2-(2-phenethyl-5-aminobenzoylamino)-4-methylsulfanylbutyrate (compound 79), used in the preparation of compound 36 was synthesised as follows;

A mixture of methyl 2-bromo-5-nitrobenzoate (10g) phenyl acetylene(4.2 ml), triethylamine  
15 (100ml), cuprous iodide(0.4g), dimethylformamide(200ml) and bis-(triphenylphosphine)-palladium(II)chloride(1.35g) was stirred at ambient temperature for 1 hour under an argon atmosphere. The solvents were removed under reduced pressure and the residue treated with 1N. hydrochloric acid(2L) and then extracted with ethyl acetate (2x300ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution(100ml),  
20 water(3x100ml) and brine(100ml) filtered through phase separating paper and evaporated to dryness. The residue was purified by flash column chromatography on silica using ethyl acetate/hexane(gradient: 0 to 10%) as eluant to give methyl 2-(2-phenylethynyl)-5-nitrobenzoate (compound 76) as a yellow solid (9.98g).

## Compound 76:

25 NMR (CDCl<sub>3</sub>)  $\delta$  : 4.02(s, 3H), 7.38-7.44(m, 3H), 7.59-7.64(m, 2H), 7.80(d, 1H), 8.33(dd, 1H), 8.84(d, 1H).

A mixture of compound 76(9.4 g), 10%Pd/C(0.94 g) and ethyl acetate(1L) was stirred under an hydrogen atmosphere at 1 bar pressure for 16 hours. The mixture was filtered through a pad  
30 of Celite and the filtrate evaporated under reduced pressure to give methyl 2-phenethyl-5-aminobenzoate (compound 77) as an oil(8.5 g) .



Compound 77:

NMR (CDCl<sub>3</sub>)  $\delta$ : 2.80-2.88(m, 2H), 3.08-3.16(m, 2H), 3.86(s, 3H), 6.73(dd, 1H), 6.98(d, 1H), 7.15-7.30(m, 6H).

5 A mixture of compound 77(8.5 g), 2N. aqueous sodium hydroxide (50 ml) and methanol(100 ml) was stirred at ambient temperature for 18 hours and then heated at reflux for 2 hours. The mixture was cooled and evaporated under reduced pressure. The product was redissolved in water (1L) and washed with diethyl ether(250 ml). The aqueous solution was acidified to pH 5-6 with glacial acetic acid . The resulting precipitate was isolated by filtration and dried  
10 under vacuum at 60°C to give a powder which was azeotroped with toluene(3x50 ml) and then dried under high vacuum to give 5-amino-2-phenethylbenzoic acid (compound 78) (8.0 g).

Compound 78:

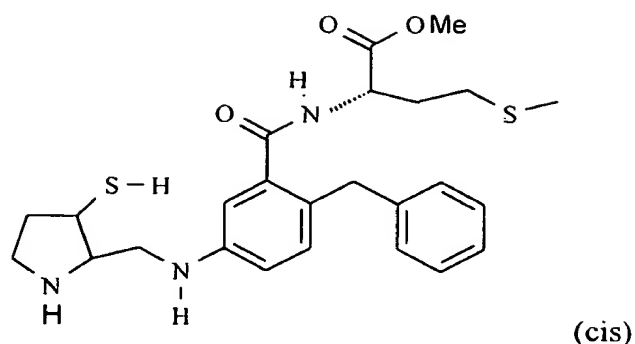
NMR (DMSO-d<sub>6</sub>)  $\delta$  : 2.68-2.76(m, 2H), 2.94-3.00(m, 2H), 6.62(dd, 1H), 6.93(d, 1H),  
15 7.05(d, 1H), 7.12-7.30(m, 5H).

A mixture of L-methionine methyl ester HCl.(12.41 g), compound 78(5g), EDC (4.77 g) and DMAP(13.61 g) in dichloromethane(250 ml) was stirred at ambient temperature for 3 hours. The dichloromethane was evaporated under reduced pressure and the residue treated with  
20 1M. aqueous citric acid solution(200 ml) and then extracted with ethyl acetate (2x100 ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate(100 ml) dried and evaporated to dryness. The product was purified on a silica flash column using ethyl acetate/iso-hexane as eluant (50:50) to give compound 79 as a solid (6.73 g).

25 Compound 79:

NMR (DMSOd<sub>6</sub>)  $\delta$ : 1.96-2.16(m, 2H), 2.03(s, 3H), 2.45-2.60(m, 4H), 2.69-2.82(m, 2H), 3.60(s, 3H), 4.53(q, 1H), 5.04(s, 2H), 6.51-6.60(m, 2H), 6.85-6.91(d, 1H), 7.13-7.28(m, 5H), 8.59(d, 1H).



Example 12

5

Compound	R <sup>1</sup>	Position of R <sup>1</sup> on phenyl	R <sup>2</sup>	Position of R <sup>2</sup> on phenyl
47	Ph-	4	Me	3
48	PhCH <sub>2</sub> -	4	Me	3
49	PhCH <sub>2</sub> CH <sub>2</sub> -	4	Me	3
50	4-F-PhCH <sub>2</sub> CH <sub>2</sub> -	3	Me	4
51	PhCH <sub>2</sub> CH <sub>2</sub> -	4	H	3
52	4-F-PhCH <sub>2</sub> CH <sub>2</sub> -	3	H	4

Compounds 51 and 52 were prepared from compounds 40 and 50 respectively using a similar method to that used to prepare compound 27 (Example 6). Compounds 47, 48, 49 and 50 were prepared by deprotecting the appropriate tritylsulfanyl compounds (compounds 43, 44, 10 45 and 46 respectively) using a similar method to that of Example 1, step 1.

Compound 47:

NMR (DMSO-d<sub>6</sub>)  $\delta$ : 1.72-1.88(m, 3H), 1.97(s, 3H), 1.97-2.35(m, 3H), 3.13-3.57(m, 5H), 3.60(s, 3H), 3.65-3.86(m, 2H), 4.30-4.40(m, 1H), 6.70(d, 1H), 6.80(dd, 1H), 7.15-7.32(m, 6H), 8.47-8.53(m, 1H), 9.43(br.s, 1H), 9.90(br.s, 1H).

15 Micro Analysis:

%Theory C51.70, H6.18, N7.54, S11.50

(2.00HCl, 0.60 H<sub>2</sub>O)

%Found C51.90, H6.10, N7.80, S11.60



## Compound 48:

NMR (DMSO- $d_6$ )  $\delta$ : 1.90-2.05(m, 3H), 2.03(s, 3H), 2.35-2.53(m, 1H), 3.15-3.55(m, 6H), 3.62(s, 3H), 3.65-3.99(m, 4H), 4.43-4.53(m, 1H), 6.63-6.70(m, 2H), 6.97(d, 1H), 7.07-7.23(m, 5H), 8.63-8.70(m, 1H), 9.39(br.s, 1H), 9.85(br.s, 1H).

5 Micro Analysis: %Theory C51.89, H6.45, N7.26  
(2.00 HCl, 1.00 H<sub>2</sub>O) %Found C51.60, H6.40, N7.20

## Compound 49:

NMR (DMSO- $d_6$ )  $\delta$ : 1.93-2.04(m, 6H), 2.35-2.92(m, 6H), 3.15-3.55(m, 5H), 3.60(s, 3H), 3.63-3.84(m, 2H), 4.50-4.60(m, 1H), 6.65-6.70(m, 2H), 6.99-7.30(m, 6H), 8.68(d, 1H),  
10 9.41(br.s, 1H), 9.90(br.s, 1H).

Micro Analysis: %Theory C53.50, H6.56, N7.20, S10.99  
(2.00HCl, 0.5 H<sub>2</sub>O) %Found C 53.30, H6.20, N7.20, S10.90

## Compound 50:

NMR (DMSO- $d_6$ )  $\delta$  1.91-2.09(m, 2H), 2.04(s, 3H), 2.33-2.65(m, 4H), 2.65-3.10(m, 5H), 3.10-  
15 3.39(m, 2H), 3.49(s, 1H), 3.60(s, 3H), 3.71(m, 2H), 4.49(q, 1H), 5.88(br.s, 2H), 6.51(m, 2H), 7.05(m, 2H), 7.24(m, 3H), 8.39(d, 1H), 9.30-9.50(br.s, 1H), 9.95(br.s, 1H).

Micro Analysis: %Theory C 51.98, H6.19, N7.00, S10.68  
(2 HCl, 0.45 H<sub>2</sub>O) %Found C51.60, H5.90, N7.40, S10.60.

## Compound 51:

20 NMR (DMSO- $d_6$ )  $\delta$ : 1.93-2.04(m, 6H), 2.35-2.87(m, 6H), 3.15-3.85(m, 7H), 4.42-4.53(m, 1H), 6.60-6.67(m, 2H), 7.00(d, 1H), 7.10-7.27(m, 5H), 8.47-8.55(m, 1H), 9.35(br.s, 1H), 9.80(br.s, 1H).

Micro Analysis: %Theory C53.60, H6.30, N7.50  
(2.00 HCl) %Found C53.50, H6.10, N7.40

## 25 Compound 52:

NMR (DMSO- $d_6$ )  $\delta$ : 1.90-2.05(m, 2H), 2.00(s, 3H), 2.38-2.58(m, 4H), 2.69-3.05(m, 5H), 3.15-3.38(m, 2H), 3.43-3.51(m, 1H), 3.69-3.75(m, 2H), 3.88-4.05(m, 1H), 4.38-4.49(q, 1H), 6.46-6.58(d, 2H), 7.06(m, 2H), 7.25(m, 3H), 8.25(d, 1H), 9.4(br.s, 1H), 9.95(br.s, 1H)

Micro Analysis: %C 50.86, H6.03, N7.12, S10.86  
30 (2HCl, 0.65 H<sub>2</sub>O) %C 50.50, H5.70, N7.20, S10.80



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The starting material was prepared as follows:

Compounds 43, 44, 45 and 46 were prepared by reacting compound 9 with the appropriate aniline using a similar method to that used to prepare compound 18 in Example 5.

Compound 43

5 NMR (DMSO-d<sub>6</sub>)  $\delta$ : 1.20-1.35(m, 9H), 1.53-1.85(m, 3H), 1.95(s, 3H), 2.10-2.30(m, 3H), 2.50-3.20(m, 6H), 3.55-3.60(m, 3H), 4.25-4.37(m, 1H), 5.30-5.58(m, 1H), 6.55-6.67(m, 2H), 7.05(d, 1H), 7.17-7.44(m, 20H), 8.35-8.47(m, 1H).

Compound 44

10 NMR (DMSO-d<sub>6</sub>)  $\delta$ : 1.17-1.33(m, 9H), 1.47-1.62(m, 1H), 1.83-2.00(m, 3H), 2.00(s, 3H), 2.02-2.50(m, 2H), 2.60-3.30(m, 6H), 3.59(s, 3H), 3.80-3.95(m, 2H), 4.43-4.52(m, 1H), 4.97-5.27(m, 1H), 6.40-6.60(m, 2H), 6.84(d, 1H), 7.05-7.43(m, 20H), 8.47-8.57(m, 1H).

Compound 45:

15 NMR (DMSO-d<sub>6</sub>)  $\delta$ : 0.83-0.95(m, 1H), 1.20-1.38(m, 9H), 1.46-1.62(m, 1H), 1.85-2.20(m, 6H), 2.45-3.27(m, 11H), 3.58(s, 3H), 4.45-4.55(m, 1H), 4.92-5.22(m, 1H), 6.40-6.63(m, 2H), 6.90(d, 1H), 7.10-7.43(m, 20H), 8.50-8.60(m, 1H).

Compound 46:

20 NMR (CDCl<sub>3</sub>)  $\delta$ : 1.41(s, 9H), 2.00-2.10(m, 1H), 2.08(s, 3H), 2.14-2.34(m, 2H), 2.47-2.63(m, 2H), 2.80-3.20(m, 8H), 3.20-3.50(m, 2H), 3.75(s, 3H), 4.13-4.21(m, 1H), 4.85(q, 1H), 5.23(br.s, 1H), 6.15-6.35(m, 3H), 6.89-6.95(t, 2H), 7.13-7.33(m, 12H), 7.41-7.51(d, 6H).

The "aniline" (compound 62) used in the preparation of compound 46 was synthesised from methyl 2-(2-(4-fluorophenyl)ethynyl)-4-nitrobenzoate by standard hydrogenation to give methyl 2-(4-fluorophenethyl)-4-aminobenzoate (compound 60). Compound 60 was hydrolysed to the corresponding benzoic acid (compound 61).

25 Compound 61 was coupled with L-methionine methyl ester hydrochloride using similar conditions to those described for the preparation of compound 79 (Example 11) to give compound 62.

Compound 60:

30 NMR (CDCl<sub>3</sub>)  $\delta$ : 2.74(t, 2H), 3.03(m, 2H), 3.71(s, 3H), 5.80(s, 2H), 6.40(s, 2H), 7.04-7.12(m, 2H), 7.23-7.31(m, 2H), 7.64(dd, 1H).



Compound 61:

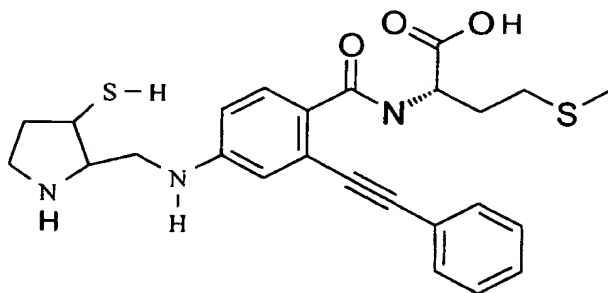
NMR (CDCl<sub>3</sub>)  $\delta$  2.87(t, 2H), 3.21(t, 2H), 6.41(s, 1H), 6.53(d, 1H), 6.91-7.00(m, 2H), 7.16-7.23(m, 2H), 8.00(d, 1H).

Compound 62:

5 NMR (CDCl<sub>3</sub>)  $\delta$  2.00-2.11(m, 1H), 2.09(s, 3H), 2.20-2.32(m, 1H), 2.57(t, 2H), 2.85(t, 2H), 2.96-3.13(m, 2H), 3.71-4.00(m, 2H), 3.77(s, 3H), 4.85(q, 1H), 6.35(d, 1H), 6.43-6.52(m, 2H), 6.91-6.96(m, 2H), 7.11-7.17(m, 2H), 7.28-7.32(m, 1H).

### Example 13

10 (2S)-2-[2-(2-(4-Fluorophenyl)ethynyl)-4-(cis-3-sulfanylpyrrolidin-2-ylmethylamino)benzoylamino]-4-methylsulfanylbutyric acid (compound 59)



Compound 59 was prepared from the corresponding methyl ester (compound 58) using a similar method to that described for the preparation of compound 20 in Example 5.

15 Compound 59:

NMR (DMSO-d<sub>6</sub>)  $\delta$  : 1.91(s, 3H), 1.91-2.04(m, 1H), 2.16-2.31(m, 1H), 2.36-2.57(m, 2H), 2.57-2.73(m, 1H), 3.16-4.20(m, 9H), 4.53(q, 1H), 6.71-7.88(m, 7H), 8.36(d, 1H), 9.55(br.m, 1H), 9.85(br.m, 1H).

Micro Analysis:

%Theory C51.06, H5.40, N7.15, S10.91

20 (2.00 HCl, 0.75 H<sub>2</sub>O)

%Found C51.20, H5.40, N7.00, S10.60

The starting material was prepared as follows ;

A mixture of compound 53 (from Example 12) (2.5 g), 2N aqueous sodium hydroxide(15 ml) and methanol(150 ml) was heated at reflux for 2 hours. The mixture was cooled and the  
25 methanol evaporated away .The residue was treated with 2N HCl (20 ml) and the mixture extracted with ethyl acetate (2x100ml). The organic extracts were combined, dried and



evaporated to dryness to give 2-[2-(4-fluorophenyl)ethynyl]-4-nitrobenzoic acid (compound 54) (2.3 g).

Compound 54 was converted to methyl (2S)-2-{2-[2-(4-fluorophenyl)ethynyl]-4-nitrobenzoylamino}-4-methylsulfanylbutyrate (compound 55) using the coupling procedure described for the preparation of compound 79 (Example 11).

Compound 55:

NMR (CDCl<sub>3</sub>)  $\delta$ : 2.00(s, 3H), 2.10-2.20(m, 1H), 2.20-2.37(m, 1H), 2.48-2.64(m, 2H), 3.76(s, 3H), 4.96(q, 1H), 7.10-7.20(m, 2H), 7.63-7.68(m, 2H), 7.84-7.97(m, 1H), 8.20-8.29(m, 2H), 8.45(d, 1H).

A mixture of compound 55 (2g), stannous chloride dihydrate(4.4 g) and ethyl acetate (150 ml) was stirred and heated at reflux for 2 hours. It was then cooled and treated dropwise with aqueous ammonia(0.880) to pH 9. The white precipitate formed was filtered and washed with more ethyl acetate(150 ml). The filtrate and washings were combined, dried and evaporated to dryness to give an oil which was purified by flash chromatography on silica using ethyl acetate/iso-hexane as eluant to give methyl (2S)-2-{2-[2-(4-fluorophenyl)ethynyl]-4-aminobenzoylamino}-4-methylsulfanylbutyrate as a yellow solid (compound 56) (1.1 g).

Compound 56:

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.99(s, 3H), 2.05-2.12(m, 1H), 2.19-2.31(m, 1H), 2.44-2.76(m, 2H), 3.91(s, 3H), 4.00(s, 2H), 4.96(q, 1H), 6.67-6.72(m, 1H), 6.85(d, 1H), 7.05-7.16(m, 2H), 7.57-7.62(m, 2H), 7.97(d, 1H), 8.05-8.12(m, 1H).

Compound 56 was reacted with compound 9 to give methyl (2S)-2-{2-(2-(4-fluorophenyl)ethynyl)-4-(1-tert-butoxycarbonyl-3-tritylsulfanylpyrrolidin-2-ylmethylamino)benzoylamino}-4-methylsulfanylbutyrate. (compound 57) using a similar method to that used to prepare compound 33.



Compound 57:

NMR (CDCl<sub>3</sub>)  $\delta$  : 1.40(s, 9H), 1.63-1.88(m, 1H), 1.96-2.08(m, 1H), 1.99(s, 3H), 2.16-2.32(m, 1H), 2.43-2.61(m, 2H), 2.80-3.55(m, 6H), 3.70(s, 3H), 4.24-4.45(m, 1H), 4.96(q, 1H), 5.45(br.s, 1H), 6.45-6.68(m, 2H), 7.08(t, 2H), 7.20-7.33(m, 10H), 7.48(d, 6H), 7.60(q, 2H), 7.96(d, 1H), 8.10(d, 1H).

Compound 57 was converted to compound 58 using a similar method to that described in Example 1, step 1.

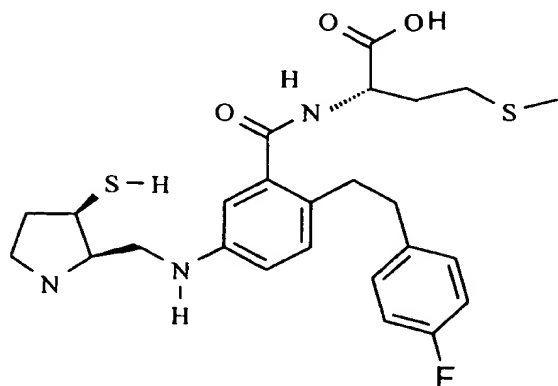
Compound 58:

NMR (DMSO-d<sub>6</sub>)  $\delta$  : 1.72-2.96(m, 6H), 1.97(s, 3H), 3.19-3.96(m, 5H), 3.71(s, 3H), 4.00-4.24(m, 1H), 4.88(q, 1H), 6.60-7.88(m, 7H), 8.08(d, 1H), 9.91(br.s, 1H)

Micro Analysis: % Theory C53.05, H5.48, N7.14, S10.90  
(2HCl) % Found C53.00, H5.60, N7.40, S11.00

#### 15 Example 14

(2S)-2-[2-(4-Fluorophenethyl)-5-([2R,3R]-3-sulfanylpyrrolidin-2-ylmethylamino)benzoylamino]-4-methylsulfanylbutyric acid (compound 73).



20 Compound 73 was prepared from the corresponding isopropyl ester (compound 72) using a similar method to that of Example 5.





Compound 73:

NMR (DMSO-d<sub>6</sub>) δ 1.91-2.08(m, 2H), 2.02 (s, 3H), 2.31-2.52(m, 4H), 2.52-2.57(m, 1H), 2.65-2.85(m, 3H), 3.27-3.48(m, 3H), 3.69-3.99(m, 5H), 4.47(m, 1H), 6.63(s, 2H), 6.93-7.08 (m, 3H), 7.16-7.23(m, 2H), 8.48(d, 1H), 9.72(br.s, 1H).

5

Micro Analysis: % Theory C49.56, H5.91, N6.94, S10.59

(2.5HCl, 0.5 H<sub>2</sub>O) % Found C49.90, H5.70, N6.90, S10.90

The starting material was prepared as follows:

- 10 A mixture of trans-3-hydroxy-L-proline (5 g), di-tert-butyl dicarbonate(9.15 g), sodium hydroxide(1.52 g), water(78 ml) and dioxan (80 ml) was stirred at 5 ° C for 30 mins. and then at ambient temperature for 16 hours. The mixture was evaporated to a smaller volume(30 ml) and diluted with water(150 ml). The pH was adjusted to 2-3 with aqueous sodium bisulphate and saturated with sodium chloride. It was then extracted with ethyl acetate(3x100 ml), the
- 15 extracts dried and the solution evaporated to dryness to give (2S,3S)-1-(tert-butoxycarbonyl)-2-carboxy-3-hydroxypyrrolidine (compound 64) as a white solid (8.42 g).

Compound 64:

NMR (DMSO-d<sub>6</sub>) δ : 1.27(2s, 9H), 1.64-1.76(m, 2H), 3.24-3.45(m, 2H), 3.92(d, 1H), 4.20(br, 1H), 5.40(br, 1H), 12.6(br, 1H).

20

- A mixture of compound 64 (8.42g), N,O-dimethyl hydroxylamine HCl(10.66 g), DMAP(26.69 g), and EDC (10.47 g) in dichloromethane(500 ml) was stirred at ambient temperature for 16 hours. The reaction mixture was then applied directly to a silica flash column and eluted with ethyl acetate to give (2S,3S)-1-(tert-butoxycarbonyl)-3-hydroxy-2-(N-methoxy-N-methylcarbamoyl)pyrrolidine (compound 65) as a clear gum(7.6 g).
- 25

Compound 65:

NMR(CDCl<sub>3</sub>) δ : 1.43(2s, 9H), 1.80-1.93(m, 1H), 2.07-2.34(m, 2H), 3.20(s, 3H), 3.53-3.72(m, 2H), 3.80(d, 3H), 4.36(br, 1H), 4.63(d, 1H).



Methane sulphonyl chloride(3.49g) was added dropwise over 10 minutes to a mixture of compound 65 (7.6 g) and triethylamine (7.7 ml) in dichloromethane (350 ml) and cooled to 0 °C under an argon atmosphere. It was then stirred at 0 °C for another hour.

The reaction mixture was then applied directly to a silica flash column which was eluted with ethyl acetate to give (2S,3S)-1-(tert-butoxycarbonyl)-2-(N-methoxy-N-methylcarbamoyl)-3-methansulfonyloxypyrrolidine (compound 66) as a gum(9.7 g).

Compound 66:

NMR (CDCl<sub>3</sub>)  $\delta$  : 1.44(2s, 9H), 2.08-2.40(m, 2H), 3.08(s, 3H), 3.23(s, 3H), 3.50-3.62(m, 1H), 3.70-3.88(m, 1H), 3.80-3.85(d, 3H), 4.92(d, 1H), 5.17(dd, 1H)

10

A solution of triphenylmethyl mercaptan (11.22 g) in DMF(150 ml) was added dropwise over 15 minutes to a suspension of sodium hydride (60% dispersion in mineral oil, 1.62 g.) in DMF(100 ml) stirred under an argon atmosphere and cooled to 5 °C. It was then stirred for a further 30 minutes. A solution of compound 66 (9.7 g) in DMF (50 ml) was then added and the reaction mixture allowed to warm to ambient temperature and stirred for a further 2 hours. It was then heated at 50 °C for 4 hours, cooled to ambient temperature and the DMF evaporated under reduced pressure. The residue was then treated with 1M. aqueous citric acid (200 ml) and extracted with ethyl acetate (3x100ml). The extracts were combined, washed with brine (100 ml), dried and evaporated under reduced pressure. The product was purified by flash column chromatography, eluting with ethyl acetate/iso-hexane(50:50) to give (2R,3R)-1-(tert-butoxycarbonyl)-2-(N-methoxy-N-methylcarbonyl)-3-tritylsulfanylprrrolidine (compound 67) as a solid foam (1.3 g).

Compound 67:

NMR (CDCl<sub>3</sub>)  $\delta$  0.91-1.01(m, 1H), 1.31(s, 9H), 2.00-2.10(m, 1H), 2.81-3.00(m, 2H), 3.30(s, 3H), 3.31-3.60(m, 1H), 3.70-4.00(d, 3H), 5.10(d, 1H), 7.11-7.30 (m, 10H), 7.50(d, 5H).

Compound 67 was reduced to (2R,3R)-1-(tert-butylcarbonyl)-2-formyl-3-tritylsulfanylprrrolidine (compound 68) with lithium aluminium hydride using a similar procedure to that described for the preparation of compound 9 in Example 1.

Compound 68:

NMR (CDCl<sub>3</sub>)  $\delta$  : 1.33(2s, 9H), 1.61-1.81(m, 1H), 1.93-2.08(m, 1H), 3.00-3.65(m, 4H), 7.21-7.35(m, 10H), 7.49(d, 5H), 9.47 (d, 1H).



Methyl 2-(4-fluorophenethyl)-5-((2R,3R)-1-(tert-butoxycarbonyl-3-tritylsulfanylpyrrolidin-2-yl)benzoate (compound 69) was prepared by reacting compound 68 with methyl 5-amino-2-(4-fluorophenethyl)benzoate (compound 75) under reductive amination conditions, similar to those described for the preparation of compound 17 in Example 5, but using methanol in place of isopropanol.

Compound 69:

NMR (CDCl<sub>3</sub>)  $\delta$  1.40(s, 9H), 2.63-3.17 (m, 9H), 3.41-3.53 (m, 1H), 3.87(s, 3H), 6.49- 6.65 (br.s, 1H), 6.88-7.00 (m, 3H), 7.00-7.07(m, 1H), 7.13-7.33 (m,12H), 7.48(d, 6H).

10

Standard base hydrolysis of compound 69 with sodium hydroxide gave the corresponding benzoic acid (compound 70).

Compound 70:

NMR (CDCl<sub>3</sub>)  $\delta$  : 1.41(s, 9H), 1.45-1.68(m, 7H), 2.79-2.96(m, 4H), 3.09-3.16(m, 3H), 6.91- 6.96(m, 3H), 7.11-7.33(m, 12H) 7.47-7.53(m, 6H).

15

Compound 70 was coupled with L-methionine isopropyl ester in dichloromethane in the presence of EDC and DMAP to give isopropyl (2S)-2-[2-(4-fluorophenethyl)-5-((2R,3R)-1-(tert-butoxycarbonyl)-3-tritylsulfanylpyrrolidin-2-ylmethylamino)benzoylamino]-4-methylsulfanylbutyrate (compound 71).

20 Compound 71:

NMR (CDCl<sub>3</sub>)  $\delta$ : 1.27(m, 6H), 1.49(2s, 9H),1.92-2.13(m, 1H), 2.05(s, 3H), 2.13-2.31(m,1H), 2.51-2.60(m, 1H), 2.78-2.99(m, 4H), 3.07-3.19(m, 1H),4.73-4.89(m, 1H), 5.00-5.13(m, 1H), 6.31-6.43(m, 1H), 6.43-6.64(m, 1H), 6.88-6.94(m, 3H), 7.09-7.16(m, 2H), 7.20-7.33(m, 10H), 7.45-7.51(m, 5H).

25

Compound 71 was deprotected with TFA and triethylsilane to give isopropyl (2S)2-[2-(4-fluorophenethyl)-5-((2R,3R)-3-sulfanylpyrrolidin-2-yl)methylamino)benzoylamino]-4-methylsulfanylbutyrate (compound 72).

Compound 72:

30 NMR (DMSO-d<sub>6</sub>)  $\delta$  : 1.13(m, 6H), 1.91-2.04(m, 2H), 2.00(s, 3H), 2.51-2.62(m, 2H), 2.65- 2.85(m, 4H), 3.12-3.53(m, 5H), 3.65-4.00(m, 2H), 4.45(q, 1H), 4.84-4.93(m, 1H), 5.60-



- 73 -

5.92(br, 4H), 6.67(s, 2H), 6.96-7.07(m, 3H), 7.16-7.23(m, 2H), 8.61(d, 1H), 9.45(br.s, 1H), 9.92(br.s, 1H).

Compound 75 was synthesised as follows ;

- 5 A mixture of methyl 2-bromo-5-nitrobenzoate (5 g), 4-fluorostyrene (3.5 g), tributylamine (0.39 g), bis-(triphenylphosphine)-palladium(II)chloride (0.3 g), sodium bicarbonate(2.65 g) and water (30 ml) was stirred and heated at reflux under an argon atmosphere for 1.5 hours. The reaction was then cooled, suspended in dichloromethane (200 ml) and passed through a pad of silica (chromatography grade) eluting with more dichloromethane The
- 10 dichloromethane was then evaporated away and the residue treated with iso-hexane (200 ml) to give methyl 2-[2-(4-fluorophenyl)ethynyl]-5-nitrobenzoate (compound 74) as a yellow precipitate which was filtered and dried, (5.05 g).

Compound 74:

- 15 NMR (CDCl<sub>3</sub>)  $\delta$ : 3.99(s, 3H), 7.08(t, 2H), 7.15(d, 1H), 7.55(q, 2H), 7.88(d, 1H), 8.0(d, 1H), 8.32(2d, 1H), 8.8(d, 1H).

- A mixture of compound 74 (29 g), 10% Pd/C (3 g), and ethyl acetate (400 ml) was stirred under an hydrogen atmosphere for 6 hours. The catalyst was removed by filtration and
- 20 replaced by fresh catalyst (3 g). The hydrogenation was then continued for another 16 hours, the catalyst was again filtered off, the filtrate evaporated to dryness and the residue treated with iso-hexane to give a white precipitate which was isolated by filtration and dried to give compound 75 (23.5 g).

25 Compound 75:

NMR (CDCl<sub>3</sub>)  $\delta$ : 2.8(t, 2H), 3.1(t, 2H), 3.62(s, 2H), 3.88(s, 3H), 6.72(dd, 1H), 6.93(m, 3H), 7.13(m, 2H), 7.23(d, 1H).





Example 15**Pharmaceutical compositions**

The following illustrate representative pharmaceutical dosage forms of the invention as defined herein (the active ingredient being termed "Compound X"), for therapeutic or  
 5 prophylactic use in humans:

(a)	<u>Tablet I</u>	<u>mg/tablet</u>
	Compound X.....	100
	Lactose Ph.Eur.....	182.75
10	Croscarmellose sodium.....	12.0
	Maize starch paste (5% w/v paste).....	2.25
	Magnesium stearate.....	3.0

(b)	<u>Tablet II</u>	<u>mg/tablet</u>
15	Compound X.....	50
	Lactose Ph.Eur.....	223.75
	Croscarmellose sodium.....	6.0
	Maize starch.....	15.0
	Polyvinylpyrrolidone (5% w/v paste).....	2.25
20	Magnesium stearate.....	3.0

(c)	<u>Tablet III</u>	<u>mg/tablet</u>
	Compound X.....	1.0
	Lactose Ph.Eur.....	93.25
25	Croscarmellose sodium.....	4.0
	Maize starch paste (5% w/v paste).....	0.75
	Magnesium stearate.....	1.0



- 75 -

(d)	<u>Capsule</u>	<u>mg/capsule</u>
	Compound X.....	10
	Lactose Ph.Eur.....	488.5
	Magnesium.....	1.5
5		
(e)	<u>Injection I</u>	<u>(50 mg/ml)</u>
	Compound X.....	5.0% w/v
	1M Sodium hydroxide solution.....	15.0% v/v
	0.1M Hydrochloric acid	
10	(to adjust pH to 7.6)	
	Polyethylene glycol 400.....	4.5% w/v
	Water for injection to 100%	
(f)	<u>Injection II</u>	<u>(10 mg/ml)</u>
15	Compound X.....	1.0% w/v
	Sodium phosphate BP.....	3.6% w/v
	0.1M Sodium hydroxide solution.....	15.0% v/v
	Water for injection to 100%	
20	(g) <u>Injection III</u> <u>(1mg/ml, buffered to pH6)</u>	
	Compound X.....	0.1% w/v
	Sodium phosphate BP.....	2.26% w/v
	Citric acid.....	0.38% w/v
	Polyethylene glycol 400.....	3.5% w/v
25	Water for injection to 100%	
(h)	<u>Aerosol I</u>	<u>mg/ml</u>
	Compound X.....	10.0
	Sorbitan trioleate.....	13.5
30	Trichlorofluoromethane.....	910.0
	Dichlorodifluoromethane.....	490.0



- 76 -

5	(i)	<u>Aerosol II</u>	<u>mg/ml</u>
		Compound X.....	0.2
		Sorbitan trioleate.....	0.27
		Trichlorofluoromethane.....	70.0
		Dichlorodifluoromethane.....	280.0
		Dichlorotetrafluoroethane.....	1094.0
10	(j)	<u>Aerosol III</u>	<u>mg/ml</u>
		Compound X.....	2.5
		Sorbitan trioleate.....	3.38
		Trichlorofluoromethane.....	67.5
		Dichlorodifluoromethane.....	1086.0
		Dichlorotetrafluoroethane.....	191.6
15	(k)	<u>Aerosol IV</u>	<u>mg/ml</u>
		Compound X.....	2.5
		Soya lecithin.....	2.7
		Trichlorofluoromethane.....	67.5
		Dichlorodifluoromethane.....	1086.0
20		Dichlorotetrafluoroethane.....	191.6
25	(l)	<u>Ointment</u>	<u>ml</u>
		Compound X.....	40 mg
		Ethanol.....	300 µl
		Water.....	300 µl
		1-Dodecylazacycloheptan-2-one.....	50 µl
		Propylene glycol.....	to 1 ml

Note

30 The above formulations may be obtained by conventional procedures well known in  
the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for



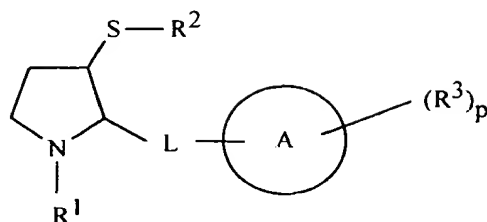
example for example to provide a coating of cellulose acetate phthalate. The aerosol formulations (h)-(k) may be used in conjunction with standard, metered dose aerosol dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80, polyglycerol oleate or oleic acid.





**CLAIMS**

A compound of the Formula I



Formula I

5 wherein:

**R¹** is selected from H; -C<sub>1-4</sub>alkyl; -CO-C<sub>1-4</sub>alkyl; -CO-O-C<sub>1-4</sub>alkyl; -CO-O-C<sub>2-4</sub>alkenyl; -C<sub>1-4</sub>alkylene-CONR<sup>4</sup>R<sup>5</sup> (wherein R<sup>4</sup> and R<sup>5</sup> are independently selected from H and C<sub>1-4</sub>alkyl); -C<sub>1-4</sub>alkylene-COOR<sup>6</sup> (wherein R<sup>6</sup> is selected from H and C<sub>1-4</sub>alkyl); -C<sub>1-3</sub>alkylene-Ph and -CO-O(CH<sub>2</sub>)<sub>n</sub>Ph wherein the phenyl groups in -C<sub>1-</sub>

10 <sub>3</sub>alkylene-Ph and -CO-O(CH<sub>2</sub>)<sub>n</sub>Ph are optionally substituted by R<sup>a</sup> and/or R<sup>b</sup> and R<sup>a</sup> and R<sup>b</sup> are independently selected from C<sub>1-4</sub>alkyl, halogen, hydroxy, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoyloxy, amino, C<sub>1-4</sub>alkylamino, di(C<sub>1-4</sub>alkyl)amino, C<sub>1-4</sub>alkanoylamino, nitro, cyano, carboxy, carbamoyl, C<sub>1-4</sub>alkoxycarbonyl, thiol, C<sub>1-4</sub>alkylsulfanyl, C<sub>1-4</sub>alkylsulfinyl, C<sub>1-4</sub>alkylsulfonyl and sulfonamido; and n=0-4;

15 **R²** is selected from H; -C<sub>1-4</sub>alkyl; -COC<sub>1-4</sub>alkyl; and -COOC<sub>1-4</sub>alkyl; and -C<sub>1-3</sub>alkylene-Ph optionally substituted on the phenyl ring by R<sup>a</sup> and/or R<sup>b</sup>;

**R³** is selected from H; OH; CN; CF<sub>3</sub>; NO<sub>2</sub>; -C<sub>1-4</sub>alkyl; -C<sub>1-4</sub>alkylene-R<sup>7</sup>; -C<sub>2-4</sub>alkenylene-R<sup>7</sup>; -C<sub>2-4</sub>alkynylene-R<sup>7</sup>; R<sup>7</sup>; OR<sup>7</sup> (where R<sup>7</sup> is selected from phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms

20 selected from O, N and S and any aryl ring in R<sup>7</sup> is optionally substituted by R<sup>a</sup> and/or R<sup>b</sup>); C<sub>2-4</sub>alkenyl; halogen; -(CH<sub>2</sub>)<sub>n</sub>COOR<sup>8</sup> (where n = 0-3 and R<sup>8</sup> represents H, C<sub>1-4</sub>alkyl, or C<sub>2-4</sub>alkenyl); -CONR<sup>9</sup>R<sup>10</sup> (where R<sup>9</sup> and R<sup>10</sup> independently represent H, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, -O-C<sub>1-4</sub>alkyl, -O-C<sub>2-4</sub>alkenyl or -C<sub>1-3</sub>alkylenePh (wherein Ph is optionally substituted by R<sup>a</sup> and R<sup>b</sup> as hereinabove defined); -CON(R<sup>11</sup>)OR<sup>12</sup> (where R<sup>11</sup> and R<sup>12</sup> independently represent H, C<sub>1-4</sub>alkyl or C<sub>2-4</sub>alkenyl);

a group of Formula II: -CONR<sup>13</sup>-CR<sup>13a</sup>R<sup>14</sup>-COOR<sup>17</sup>, (where R<sup>13</sup> and R<sup>13a</sup> are independently H or C<sub>1-4</sub>alkyl, R<sup>17</sup> is H or C<sub>1-6</sub>alkyl, R<sup>14</sup> is selected from the side chain of a lipophilic



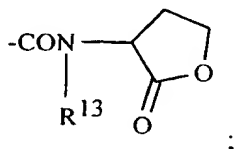
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amino acid, carbamoylC<sub>1-4</sub>alkyl, N-(monoC<sub>1-4</sub>alkyl)carbamoylC<sub>1-4</sub>alkyl and N-(diC<sub>1-4</sub>alkyl)carbamoylC<sub>1-4</sub>alkyl) the group of Formula II having L or D configuration at the chiral alpha carbon in the corresponding free amino acid; a lactone of formula:



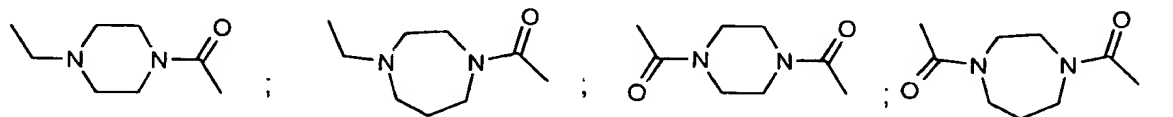
C<sub>1-4</sub>alkyl monosubstituted on carbon with =N-OH;

a group of Formula -X-R<sup>15</sup> (where X is selected from O, CO, CH<sub>2</sub>, S, SO, SO<sub>2</sub> and R<sup>15</sup> is selected from C<sub>1-6</sub>alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and any aryl ring in

10 R<sup>15</sup> is optionally substituted by R<sup>a</sup> and/or R<sup>b</sup>;

p is 0-3 in which R<sup>3</sup> values can be the same or different;

L is a linking moiety selected from the following groups written from left to right in Formula I:



15 (wherein the piperazine and perhydro-1,4-diazepine rings are optionally substituted);

-CO-NR<sup>16</sup>-; -CH<sub>2</sub>-NR<sup>16</sup>-; -CH<sub>2</sub>S-; -CH<sub>2</sub>O-; -CH<sub>2</sub>-CHR<sup>16</sup>; -CH=CR<sup>16</sup>-; -CH<sub>2</sub>NR<sup>16</sup>-T-;

-CH<sub>2</sub>NR<sup>16</sup>-SO<sub>2</sub>-; -CH<sub>2</sub>-NR<sup>16</sup>-CO-T<sup>1</sup>-; -CO-NR<sup>16</sup>-T-; -CH<sub>2</sub>S-T-; -CH<sub>2</sub>O-T- (where R<sup>16</sup> is selected from H, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylene-Z, -CO-C<sub>1-4</sub>alkylene-Z, -CO-C<sub>1-6</sub>alkyl, -COZ, Z and Z is selected from -O-C<sub>1-4</sub>alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or

20 bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and any aryl ring in R<sup>16</sup> is optionally substituted by R<sup>a</sup> and/or R<sup>b</sup> as hereinabove defined;

where, T represents -(CH<sub>2</sub>)<sub>m</sub>- where m is 1-4 and T is optionally monosubstituted with any value of R<sup>16</sup> other than H; and

where T<sup>1</sup> represents -(CH<sub>2</sub>)<sub>m<sup>1</sup></sub>- wherein m<sup>1</sup> is 0-4 and T is optionally monosubstituted with

25 any value of R<sup>16</sup> other than H);



A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms where the heteroatoms are independently selected from O, N & S;

or a -S-S- dimer thereof when  $R^2=H$ ; or a N-oxide thereof;

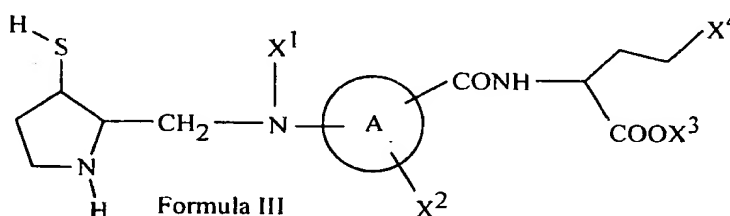
5 or a pharmaceutically acceptable salt, prodrug or solvate thereof.

2. A compound according to claim 1 wherein L is  $-\text{CH}_2\text{N}(\text{R}^{16})-$  or  $-\text{CH}_2\text{N}(\text{R}^{16})\text{T}-$ .

3 A compound according to either claim 1 or claim 2 wherein A is phenyl or naphthyl.

4. A compound according to claim 1 of the formula (III):

10



wherein:

$\text{X}^1$  is selected from H;  $\text{C}_1$ -6alkyl; hydroxy $\text{C}_1$ -6alkyl,  $\text{C}_1$ -6alkoxy $\text{C}_1$ -6alkyl;  $\text{C}_1$ -6alkylcarbonyl; hydroxy $\text{C}_1$ -6alkylcarbonyl;  $\text{C}_1$ -6alkoxy $\text{C}_1$ -6alkylcarbonyl;

15 A is selected from phenyl, naphthyl or a 5-10 membered heterocyclic ring having upto 5 heteroatoms selected from O, N and S;

$\text{X}^2$  is selected from H; phenyl; phenyl $\text{C}_1$ -6alkyl; a 5-6 membered heteroaryl ring containing upto 3 heteroatoms selected from O, N and S optionally linked to A by  $\text{C}_1$ -6alkyl; and  $\text{X}^2$  is optionally substituted on any ring by  $\text{R}^a$  and/or  $\text{R}^b$  as defined in claim 1;

20  $\text{X}^3$  is selected from H;  $\text{C}_1$ -6alkyl;

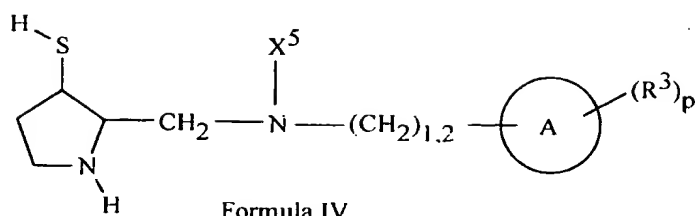
$\text{X}^4$  is selected from  $\text{C}_1$ -6alkylsulfanyl;  $\text{C}_1$ -6alkylsulfinyl;  $\text{C}_1$ -6alkylsulfonyl; carbamoyl; N-( $\text{C}_1$ -6alkyl)carbamoyl; N-(di $\text{C}_1$ -6alkyl)carbamoyl; and hydroxy or a  $\text{C}_1$ -4alkyl ether thereof; or a N-oxide pharmaceutically-acceptable salt, prodrug or solvate thereof.

5. A compound according to claim 1 of the formula (IV):

25



- 81 -



wherein:

$X^5$  is selected from  $C_{1-4}$ alkyloxy $C_{1-4}$ alkyl;  $-C_{1-4}$ alkylPh;  $-\text{CO}-C_{1-4}$ alkyl-Ph;  $-\text{CO}-C_{1-6}$ alkyl;  $-\text{CO}-C_{1-4}$ alkyl-heteroaryl where heteroaryl is a 5-10 membered heteroaryl ring containing 5 upto 5 heteroatoms selected from O, N and S and Ph or heteroaryl are optionally substituted by  $R^a$  and/or  $R^b$  as defined in claim 1;

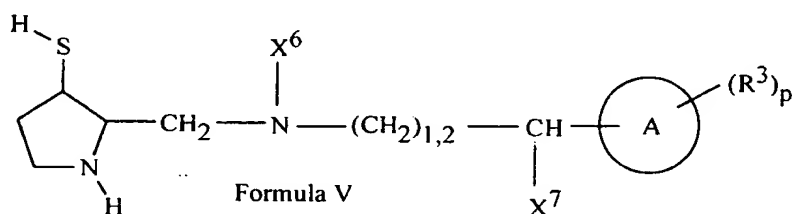
$C_{1-4}$ alkyloxy $C_{1-4}$ alkyl;

A is naphthyl or a 10 membered heteroaryl ring having upto 5 heteroatoms selected from O, N and S;

10  $R^3$  and p are as defined in claim 1;

or a N-oxide or a pharmaceutically-acceptable salt, prodrug or solvate thereof.

6. A compound according to claim 1 of the formula (V):



15 wherein:

$X^6$  has any value defined for  $X^5$  in claim 5;

$X^7$  is Ph optionally substituted by  $R^a$  and/or  $R^b$  as defined in claim 1;

A is Ph or naphthyl or a 5-10 membered heteroaryl ring having upto 5 heteroatoms selected from O, N and S;

20  $R^3$  and p are as defined in claim 1;

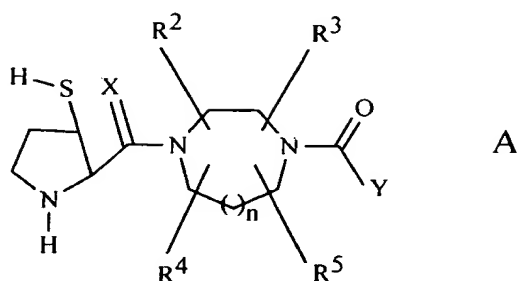
or a N-oxide, or a pharmaceutically acceptable salt, prodrug or solvate thereof.

7. A compound of the formula A:





- 82 -



wherein:

5 X is O or H<sub>2</sub>;

n is 0 or 1;

t is 1 to 4;

R<sup>2'</sup>, R<sup>3'</sup>, R<sup>4'</sup>, and R<sup>5'</sup> are independently selected from: H; C<sub>1</sub>-8alkyl, alkenyl, alkynyl, aryl, heterocycle, -CO-NR<sup>6'</sup>R<sup>7'</sup> or -CO-OR<sup>6'</sup>, unsubstituted or substituted with one or more of:

10 1) aryl or heterocycle, unsubstituted or substituted with:

- a. C<sub>1</sub>-4alkyl,
- b. (CH<sub>2</sub>)<sub>t</sub>OR<sup>6'</sup>,
- c. (CH<sub>2</sub>)<sub>t</sub>NR<sup>6'</sup>R<sup>7'</sup>,
- d. halogen,

15 2) C<sub>3</sub>-6cycloalkyl,

3) OR<sup>6'</sup>,

4) SR<sup>6'</sup>, S(O)R<sup>6'</sup>, SO<sub>2</sub>R<sup>6'</sup>,

5) -NR<sup>6'</sup>R<sup>7'</sup>,

6) -NR<sup>6'</sup>-CO-R<sup>7'</sup>,

20 7) -NR<sup>6'</sup>-CO-NR<sup>7'</sup>R<sup>8'</sup>,

8) -O-CO-NR<sup>6'</sup>R<sup>7'</sup>,

9) -O-CO-OR<sup>6'</sup>,

10) -O-NR<sup>6'</sup>R<sup>7'</sup>,

11) -SO<sub>2</sub>NR<sup>6'</sup>R<sup>7'</sup>,

25 12) -NR<sup>6'</sup>-SO<sub>2</sub>-R<sup>7'</sup>,

13) -CO-R<sup>6'</sup>, or



14)  $-\text{CO}-\text{OR}^{6'}$ ;

and any two of  $\text{R}^{2'}$ ,  $\text{R}^{3'}$ ,  $\text{R}^{4'}$ , and  $\text{R}^{5'}$  are optionally attached to the same carbon atom;

Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

- 1)  $\text{C}_{1-4}$ alkyl, unsubstituted or substituted with:
  - 5 a.  $\text{C}_{1-4}$ alkoxy,
  - b.  $\text{NR}^{6'}\text{R}^{7'}$ ,
  - c.  $\text{C}_{3-6}$ cycloalkyl,
  - d. aryl or heterocycle,
  - e.  $\text{HO}$ ,
- 10 2) aryl or heterocycle,
- 3) halogen,
- 4)  $\text{OR}^{6'}$ ,
- 5)  $\text{NR}^{6'}\text{R}^{7'}$ ,
- 6)  $\text{CN}$
- 15 7)  $\text{NO}_2$ , or
- 8)  $\text{CF}_3$ ;

$\text{R}^{6'}$ ,  $\text{R}^{7'}$  and  $\text{R}^{8'}$  are independently selected from: H;  $\text{C}_{1-4}$ alkyl,  $\text{C}_{3-6}$ cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

- 20 a)  $\text{C}_{1-4}$ alkoxy,
- b) aryl or heterocycle,
- c) halogen,
- d)  $\text{HO}$ ,
- e)  $-\text{CO}-\text{R}^{9'}$ ,
- 25 f)  $-\text{SO}_2\text{R}^{9'}$ , or
- g)  $\text{NRR}^1$ , wherein

$\text{R}^{6'}$  and  $\text{R}^{7'}$  may be joined in a ring, and

$\text{R}^{7'}$  and  $\text{R}^{8'}$  may be joined in a ring;

30  $\text{R}^{9'}$  is  $\text{C}_{1-4}$ alkyl or aralkyl;

a pharmaceutically acceptable salt thereof.



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8. A compound according to claim 1 which is any one of the following individual compounds or a pharmaceutically acceptable salt thereof:

- (2S)-2-{2-benzyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester ;
- (2S)-2-{2-benzyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid ;
- (2S)-2-({2-phenyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester;
- 10 (2S)-2-({2-phenyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid;
- (2S)-2-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-naphthalene-1-carbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester ;
- (2S)-2-({3-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-naphthalene-1-carbonyl}-amino)-4-methylsulfanylbutyric acid ;
- 15 (2S)-2-({3-phenyl-5[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester;
- (2S)-2-({3-phenyl-5[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid;
- 20 (cis)-2-[N-(4-methoxybenzyl)-N-(naphthalen-1-ylmethylamino)-methyl]-pyrrolidine-3-thiol ;
- N-(naphthalen-1-ylmethyl)-N-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl]-pentanamide;
- N-(naphthalen-1-ylmethyl)-N-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl]-2-(pyridin-3-yl)-acetamide ;
- 25 N-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl]-3-methyl-N-(2-naphthalen-1-yl-ethyl)butyramide ;
- N-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl)-N-(2-naphthalen-1-yl-ethyl)-2-pyridin-3-yl-acetamide ;
- (cis)-2-{{3-methoxypropyl)-(2-naphthalen-1-ylethyl)amino}methyl}-pyrrolidine-3-thiol;
- N-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl)-2-(4-methoxy-phenyl)-N-(2-naphthalen-2-yl-ethyl)-acetamide;
- 30



(cis)-2-{{(2-(4-methoxyphenyl)ethyl)-(2-naphthalen-1-ylethyl)amino} methyl}-pyrrolidine-3-thiol;

N-(2,2-diphenyl-ethyl)-N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl]-3-methyl-butyramide ;

N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl]-3,3-dimethyl-N-(2-naphthalen-2-yl-ethyl)-  
5 butyramide;

N-(2,2-diphenyl-ethyl)-N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl]-3,3-dimethyl-butyramide;

(2S)-2-{3-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl]-(3-methoxy-propyl)-amino}-benzoylamino}-4-methylsulfanyl-butyric acid ;

N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl]-3,3-dimethyl-N-(2-naphthalen-1-yl-ethyl)-  
10 butyramide;

(2S)-4-carbamoyl-2-({2-phenyl-5-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino)-butyric acid;

(2S)-4-carbamoyl-2-({2-phenyl-5-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino)-butyric acid methyl ester;

15 2-(3-pyridyl)-N-(2,2-diphenyl-ethyl)-N-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl]-acetamide;  
6-methoxy-1-oxido-N-(2,2-diphenyl-ethyl)-N-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl]-pyridine-3-carboxamide;

N-(naphthyl-1-yl-ethyl)-N-[(cis)-3-sulfanylpyrrolidin-2-yl-methyl]-thiazole-5-carboxamide;  
6-methoxy-1-oxido-N-(naphthyl-1-yl-ethyl)-N-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl]-

20 pyridine-3-carboxamide;

(2S)-2-{2-benzyl-4-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl]amino}-benzoylamino}-4-methylsulfanyl-butyric acid;

(2S)-2-(2-methoxy-ethyl)-1-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl]-4-naphthoyl-piperazine;

(2S)-2-{2-benzyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl]amino}-benzoylamino}-4-

25 methylsulfanylbutyric acid;

(2S)-2-{2-benzyl-4-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl]amino}-benzoylamino}-4-methylsulfanylbutyric acid;

(2S)-2-{2-phenethyl-5-[(trans)-3-sulfanylpyrrolidin-2-ylmethylaminobenzoylamino]-4-methylsulfanylbutyric acid;

30 (2S)-2-{phenethyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid;



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- (2S)-2-{2-benzyl-5-[(trans)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid;
- (2S)-2-{2-(phenethyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino)-4-methylsulfanylbutyric acid;
- 5 (2S)-2-{2-(4-methylphenylethynyl)-4-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid;
- (2S)-2-{2-benzyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid isopropyl ester;
- (2S)-2-{2-benzyl-4-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-
- 10 methylsulfanylbutyric acid methyl ester;
- (2S)-2-{2-benzyl-4-[(trans)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
- (2S)-2-{2-benzyl-5-[(trans)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
- 15 (2S)-2-{2-phenyl-5-[(trans)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
- (2S)-2-{2-phenyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
- (2S)-2-{2-benzyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-
- 20 methylsulfanylbutyric acid methyl ester;
- (2S)-2-{2-(4-methylphenethyl)-4-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
- (2S)-2-{2-(4-methylphenylethynyl)-4-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
- 25 (2S)-2-(2-methoxyethyl)-1-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl]-4-(naphth-1-oyl)piperazine;
- (cis)-2-[N-isovaleryl-N-(2-(naphth-1-yl)ethyl)aminomethyl]-3-sulfanylpyrrolidine;
- (cis)-2-[N-(3-pyridylacetyl)-N-(naphth-1-yl)ethyl]aminomethyl]-3-sulfanylpyrrolidine;
- (cis)-2-[N-1-oxido-6-methoxypyridin-3-ylcarbonyl]-N-(naphth-1-yl)ethyl]aminomethyl]-3-
- 30 sulfanylpyrrolidine;
- (cis)-2-[N-thiazol-5-ylcarbonyl]-N-(naphth-1-yl)ethyl]aminomethyl]-3-sulfanylpyrrolidine;



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- (2S)-2-[2-(4-fluorophenethyl)-4-[(cis)-3-sulfanyl]-pyrrolidin-2-ylmethylamino]benzoylamino]-4-methylsulfanylbutyric acid;  
 methyl (2S)-2-[2-(4-fluorophenethyl)-4-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]benzoylamino]-4-methylsulfanylbutyrate;
- 5 (2S)-2-[2-(4-fluorophenethyl)-4-((2R,3R)-3-sulfanylpyrrolidin-2-ylmethylamino)benzoylamino]-5-methylsulfanylbutyric acid;  
 (2S)-2-{2-Benzyl-5-[[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester ;  
 (2S)-2-{2-Benzyl-5-[[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-
- 10 methylsulfanylbutyric acid ;  
 (2S)-2-({2-phenyl-5-[[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester;  
 (2S)-2-({2-phenyl-5-[[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid;
- 15 (2S)-2-({3-[[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-naphthalene-1-carbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester ;  
 (2S)-2-({3-[[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-naphthalene-1-carbonyl}-amino)-4-methylsulfanylbutyric acid ;  
 (2S)-2-({3-phenyl-5[[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-
- 20 amino)-4-methylsulfanylbutyric acid methyl ester;  
 (2S)-2-({3-phenyl-5[[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid;  
 (2R,3R)-2-[N-(4-methoxybenzyl)-N-(naphthalen-1-ylmethyl)-amino}-methyl]-pyrrolidine-3-thiol ;
- 25 N-(naphthalen-1-ylmethyl)-N-([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-pentanamide;  
N-(naphthalen-1-ylmethyl)-N-([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-2-(pyridin-3-yl)-acetamide ;  
N-([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-3-methyl-N-(2-naphthalen-1-yl-ethyl)butyramide ;
- 30 N-([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-N-(2-naphthalen-1-yl-ethyl)-2-pyridin-3-yl-acetamide ;



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(2R,3R)-2-{[(3-Methoxypropyl)-(2-naphthalen-1-ylethyl)amino]methyl}-pyrrolidine-3-thiol;  
N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-2-(4-methoxy-phenyl)-N-(2-naphthalen-2-yl-ethyl)-acetamide ;

(2R,3R)-2-{[(2-(4-Methoxyphenyl)ethyl)-(2-naphthalen-1-ylethyl)amino] methyl}-

5 pyrrolidine-3-thiol ;

N-(2,2-Diphenyl-ethyl)-N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-butyramide ;

N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-2-yl-ethyl)-butyramide ;

N-(2,2-Diphenyl-ethyl)-N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-

10 butyramide ;

(2S)-2-{3-[(2R,3R)-3-sulfanyl-pyrrolidin-2-ylmethyl)-(3-methoxy-propyl)-amino]-benzoylamino}-4-methylsulfanyl-butyric acid ;

N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-1-yl-ethyl)-butyramide ;

15 (2S)-4-carbamoyl-2-({2-phenyl-5-[(2R,3R)-3-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-butyric acid;

(2S)-4-carbamoyl-2-({2-phenyl-5-[(2R,3R)-3-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-butyric acid methyl ester;

2-(3-pyridyl)-N-(2,2-diphenyl-ethyl)-N-((2R,3R)-3-sulfanylprrrolidin-2-ylmethyl)-

20 acetamide;

6-methoxy-1-oxido-N-(2,2-diphenyl-ethyl)-N-((2R,3R)-3-sulfanylprrrolidin-2-ylmethyl)-pyridine-3-carboxamide;

N-(naphthyl-1-yl-ethyl)-N-([2R,3R]-3-sulfanylprrrolidin-2yl-methyl)-thiazole-5-carboxamide;

25 6-methoxy-1-oxido-N-(naphthyl-1-yl-ethyl)-N-((2R,3R)-3-sulfanylprrrolidin-2-ylmethyl)-pyridine-3-carboxamide;

(2S)-2-{2-benzyl-4-[(2R,3R)-3-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanyl-butyric acid; and

(2S)-2-(2-methoxy-ethyl)-1-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-4-naphthoyl-

30 piperazine.



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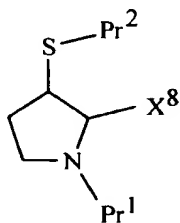
9. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 8 and a pharmaceutically-acceptable carrier.

10. A method of inhibiting farnesylation of mutant ras gene in a patient requiring such treatment by administering an effective amount of a compound of the formula (I) to the patient.

11. A compound according to any one of claims 1 to 8 for use as a medicament.

12. A compound according to any one of claims 1 to 8 for use in the preparation of a medicament for treatment of a disease mediated through farnesylation of mutant ras.

13. A process for preparing compounds of the Formula I as defined in claim 1 which comprises deprotecting a compound of Formula VI:



Formula VI

wherein X<sup>8</sup> represents the right hand side of the Formula I as defined in claim 1, Pr<sup>1</sup> is H or an amino protecting group, Pr<sup>2</sup> is H or a thio protecting group and any functional groups in X<sup>8</sup> are optionally protected with the proviso that there is at least one protecting group and optionally, if desired, converting the product thus obtained into a pharmaceutically-acceptable salt thereof.







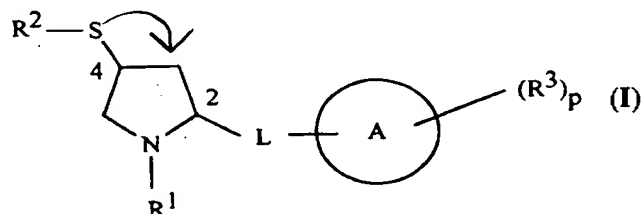
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<b>(21) International Application Number:</b> PCT/GB96/01810 <b>(22) International Filing Date:</b> 30 July 1996 (30.07.96) <b>(30) Priority Data:</b> 9515975.2      4 August 1995 (04.08.95)      GB <b>(71) Applicant (for all designated States except US):</b> ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BOYLE, Francis, Thomas [GB/GB]; ZENECA Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). DAVIES, David, Huw [GB/GB]; ZENECA Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). KENNY, Peter, Wedderburn [GB/GB]; ZENECA Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). MATUSIAK, Zbigniew, Stanley [GB/GB]; ZENECA Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). SC-HOLES, Peter, Beverley [GB/GB]; ZENECA Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). WARDLEWORTH, James, Michael [GB/GB];		ZENECA Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). <b>(74) Agent:</b> GILES, Allen, Franck: Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). <b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). <b>Published</b> <i>With international search report.</i>

**(54) Title:** 4-MERCAPTOPYRROLIDINE DERIVATIVES AS FARNESYL TRANSFERASE INHIBITORS

**(57) Abstract**

Pharmaceutical compositions comprising an inhibitor of ras farnesylation of formula (I) wherein, R<sup>1</sup> is for example H and further values as defined in the specification; R<sup>2</sup> is for example H and further values as defined in the specification; R<sup>3</sup> is for example H or a substituent having values as defined in the specification; p is 0-3 in which R<sup>3</sup> values can be the same or different; L is a linking moiety for example -CO-NH<sub>2</sub>- and further values as defined in the specification; A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms where the heteroatoms are independently selected from O, N and S; or a -S-S- dimer thereof when R<sup>2</sup>=H; or an enantiomer, diastereoisomer, pharmaceutically acceptable salt, prodrug or solvate thereof together with a pharmaceutically acceptable diluent or carrier. A particular use is cancer therapy.



or a -S-S- dimer thereof when R<sup>2</sup>=H; or an enantiomer, diastereoisomer, pharmaceutically acceptable salt, prodrug or solvate thereof together with a pharmaceutically acceptable diluent or carrier. A particular use is cancer therapy.

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GA	Gabon			VN	Viet Nam

- 1 -

#### 4-MERCAPTOPYRROLIDINE DERIVATIVES AS FARNESYL TRANSFERASE INHIBITORS

This invention relates to compounds that inhibit farnesylation of mutant ras gene products through inhibition of the enzyme farnesyl-protein transferase (FPTase). The invention also relates to methods of manufacturing the compounds, pharmaceutical compositions and methods of treating diseases, especially cancer, which are mediated through farnesylation of ras.

Cancer is believed to involve alteration in expression or function of genes controlling cell growth and differentiation. Whilst not wishing to be bound by theoretical considerations the following text sets out the scientific background to ras in cancer. Ras genes are frequently mutated in tumours. Ras genes encode guanosine triphosphate (GTP) binding proteins which are believed to be involved in signal transduction, proliferation and malignant transformation. H-, K- and N-ras genes have been identified as mutant forms of ras (Barbacid M. Ann. Rev. Biochem. 1987, 56: 779-827). Post translational modification of ras protein is required for biological activity. Farnesylation of ras catalysed by FPTase is believed to be an essential step in ras processing. It occurs by transfer of the farnesyl group of farnesyl pyrophosphate (FPP) to a cysteine at the C-terminal tetrapeptide of ras in a structural motif called the CAAX box. After further post-translational modifications, including proteolytic cleavage at the cysteine residue of the CAAX box and methylation of the cysteine carboxyl, ras is able to attach to the cell membrane for relay of growth signals to the cell interior. In normal cells activated ras is believed to act in conjunction with growth factors to stimulate cell growth. In tumour cells it is believed that mutations in ras cause it to stimulate cell division even in the absence of growth factors (Travis J. Science 1993, 260: 1877-1878), possibly through being permanently in GTP activated form rather than cycled back to GDP inactivated form. Inhibition of farnesylation of mutant ras gene products will stop or reduce activation.

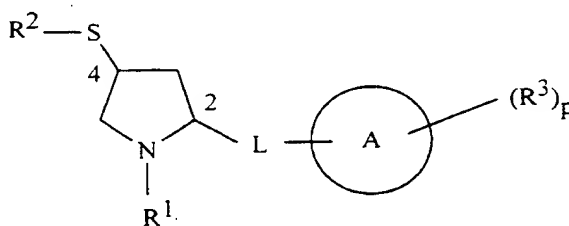
One class of known inhibitors of farnesyl transferase is based on farnesyl pyrophosphate analogues: see for example European patent application EP 534546 from Merck. Inhibitors of farnesyl transferase based on mimicry of the CAAX box have been reported. Reiss (1990) in Cell 62, 81-8 disclosed tetrapeptides such as CVIM (Cys-Val-Ile-Met). James (1993) in Science 260, 1937-1942 disclosed benzodiazepine based

- 2 -

peptidomimetic compounds. After earliest priority date of the present invention Lerner (1995) in J. Biol. Chem. 270, 26802 and Eisai in International Patent Application WO 95/25086 disclosed further peptidomimetic compounds based on Cys as the first residue. Also after the earliest priority date of the present invention Bristol-Myers Squibb in

5 European Patent Application EP 696593 disclosed for the first time farnesyl transferase inhibitors having a 4-sulfanylpyrrolidine residue in the first position.

According to one aspect of the present invention there is provided a pharmaceutical composition comprising an inhibitor of ras farnesylation of Formula I



Formula I

10 wherein:

$R^1$  is selected from H;  $-C_{1-4}$ alkyl;  $-C_{1-3}$ alkylene-Ph optionally mono or di-substituted on Ph with substituents selected from  $C_{1-4}$ alkyl, halogen, OH,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkanoyl,  $C_{1-4}$ alkanoyloxy, amino,  $C_{1-4}$ alkylamino, di( $C_{1-4}$ alkyl)amino,  $C_{1-4}$ alkanoylamino, nitro, cyano, carboxy, carbamoyl,  $C_{1-4}$ alkoxycarbonyl, thiol,  $C_{1-4}$ alkylsulfanyl,

15  $C_{1-4}$ alkylsulfinyl,  $C_{1-4}$ alkylsulfonyl and sulfonamido;  $-\text{CO}-C_{1-4}$ alkyl;  $-\text{CO}-\text{O}-C_{1-4}$ alkyl;  $-\text{CO}-\text{O}-C_{2-4}$ alkenyl;  $-\text{CO}-\text{O}-(\text{CH}_2)_n\text{Ph}$  optionally substituted on Ph as defined for substitution on Ph in  $R^1 = -C_{1-3}$ alkylene-Ph above and  $n=0-4$ ;

$-C_{1-4}$ alkylene- $\text{CONR}^4\text{R}^5$  where  $R^4$  &  $R^5$  are independently selected from H and  $C_{1-4}$ alkyl; and  $-C_{1-4}$ alkylene- $\text{COOR}^6$  where  $R^6$  is selected from H,  $C_{1-4}$ alkyl;

20  $R^2$  is selected from H;  $-C_{1-4}$ alkyl;  $-C_{1-3}$ alkylene-Ph optionally substituted on Ph as defined for substitution on Ph in  $R^1 = -C_{1-3}$ alkylene-Ph above;  $-\text{COC}_{1-4}$ alkyl; and  $-\text{COOC}_{1-4}$ alkyl;

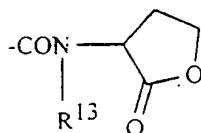
$R^3$  is selected from H; OH; CN;  $\text{CF}_3$ ;  $\text{NO}_2$ ;  $-C_{1-4}$ alkyl;  $-C_{1-4}$ alkylene- $R^7$  where  $R^7$  is selected from phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring

25 containing upto 5 heteroatoms selected from O, N and S and any aryl ring in  $R^7$  is optionally substituted as defined for substitution on the Ph group in  $R^1 = -C_{1-3}$ alkylene-Ph above;  $R^7$ ;  $C_{2-4}$ alkenyl; halogen;  $-(\text{CH}_2)_n\text{COOR}^8$  where  $n=0-3$  and  $R^8$  represents H,

SUBSTITUTE SHEET (RULE 26)

- 3 -

- $C_{1-4}$ alkyl, or  $C_{2-4}$ alkenyl;  $-\text{CONR}^9\text{R}^{10}$  where  $\text{R}^9$  and  $\text{R}^{10}$  independently represent H,  $C_{1-4}$ alkyl,  $C_{2-4}$ alkenyl,  $-\text{O}-C_{1-4}$ alkyl,  $-\text{O}-C_{2-4}$ alkenyl,  $-C_{1-3}$ alkylenePh optionally substituted as defined for this group for  $\text{R}^1$  above;  $-\text{CON}(\text{R}^{11})\text{OR}^{12}$  where  $\text{R}^{11}$  and  $\text{R}^{12}$  independently represent H,  $C_{1-4}$ alkyl and  $C_{2-4}$ alkenyl;
- 5 a group of Formula II,  $-\text{CONR}^{13}-\text{CHR}^{14}-\text{COOR}^{17}$ , where  $\text{R}^{13}$  is H or  $C_{1-4}$ alkyl,  $\text{R}^{17}$  is H or  $C_{1-6}$ alkyl,  $\text{R}^{14}$  is selected from the side chain of a lipophilic amino acid, carbamoyl $C_{1-4}$ alkyl,  $\text{N}-(\text{mono}C_{1-4}\text{alkyl})\text{carbamoyl}C_{1-4}\text{alkyl}$  and  $\text{N}-(\text{di}C_{1-4}\text{alkyl})\text{carbamoyl}C_{1-4}\text{alkyl}$ , the group of Formula II having  $\text{L}$  or  $\text{D}$  configuration at the chiral alpha carbon in the corresponding free amino acid; a lactone of formula



10

- $C_{1-4}$ alkyl monosubstituted on carbon with  $=\text{N}-\text{OH}$ ;
- a group of Formula  $-\text{X}-\text{R}^{15}$  where  $\text{X}$  is selected from O, CO,  $\text{CH}_2$ , S, SO,  $\text{SO}_2$  and  $\text{R}^{15}$  is selected from  $C_{1-6}$ alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and any aryl ring in
- 15  $\text{R}^{15}$  is optionally substituted as defined for the Ph group in  $\text{R}^1 = -C_{1-3}\text{alkylene}-\text{Ph}$ ;
- $p$  is 0-3 in which  $\text{R}^3$  values can be the same or different;

$\text{L}$  is a linking moiety selected from the following groups written from left to right in Formula I:

- $-\text{CO}-\text{NR}^{16}-$  where  $\text{R}^{16}$  is selected from H,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkylene-Z,  $-\text{CO}-$
- 20  $C_{1-4}$ alkylene-Z,
- $-\text{CO}-C_{1-6}\text{alkyl}$ ,  $-\text{COZ}$ , Z and Z is selected from  $-\text{O}-C_{1-4}\text{alkyl}$ , phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and any aryl ring in  $\text{R}^{16}$  is optionally substituted as defined for the Ph group in  $\text{R}^1 = -C_{1-3}\text{alkylene}-\text{Ph}$ ;  $-\text{CH}_2-\text{NR}^{18}-$  where  $\text{R}^{18}$  represents any value defined for
- 25  $\text{R}^{16}$ ;  $-\text{CH}_2\text{S}-$ ;  $-\text{CH}_2\text{O}-$ ;  $-\text{CH}_2-\text{CHR}^{19}-$  where  $\text{R}^{19}$  represents any value defined for  $\text{R}^{16}$ ;
- $-\text{CH}=\text{CR}^{20}-$  where  $\text{R}^{20}$  represents any value defined for  $\text{R}^{16}$ ;  $-\text{CH}_2\text{NR}^{21}-\text{T}-$  where  $\text{R}^{21}$  represents any value defined for  $\text{R}^{16}$ , T represents  $-(\text{CH}_2)_n-$  where  $n$  is 1-4 and T is optionally monosubstituted with  $\text{R}^{22}$  where  $\text{R}^{22}$  represents any value for  $\text{R}^{16}$  other than H;
- $-\text{CH}_2\text{NR}^{23}-\text{SO}_2-$  where  $\text{R}^{23}$  represents any value defined for  $\text{R}^{16}$ ;  $-\text{CH}_2-\text{NR}^{24}-\text{CO}-\text{T}-$  where

**SUBSTITUTE SHEET (RULE 26)**

- 4 -

$R^{24}$  represents any value defined for  $R^{16}$ . T represents  $-(CH_2)_n-$  where n is 0-4 and T is optionally monosubstituted with  $R^{29}$  where  $R^{29}$  represents any value for  $R^{16}$  other than H:  $-CO-NR^{25}-T-$  where  $R^{25}$  represents any value defined for  $R^{16}$ . T represents  $-(CH_2)_n-$  where n is 1-4 and T is optionally monosubstituted with  $R^{26}$  where  $R^{26}$  represents any value for  $R^{16}$  other than H;  $-CH_2S-T-$  where T represents  $-(CH_2)_n-$  where n is 1-4 and T is optionally monosubstituted with  $R^{27}$  where  $R^{27}$  represents any value for  $R^{16}$  other than H;  $-CH_2O-T-$  where T represents  $-(CH_2)_n-$  where n is 1-4 and T is optionally monosubstituted with  $R^{28}$  where  $R^{28}$  represents any value for  $R^{16}$  other than H:

A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms where the heteroatoms are independently selected from O, N & S:

or a  $-S-S-$  dimer thereof when  $R^2=H$ ; or a  $N$ -oxide thereof;

or an enantiomer, diastereoisomer, pharmaceutically acceptable salt, prodrug or solvate thereof together with a pharmaceutically acceptable diluent or carrier.

15 Preferably  $R^1$  is selected from H;  $-CO-O-(CH_2)_nPh$  optionally substituted on Ph as defined for  $R^1 = -C_{1-3}alkylene-Ph$  and  $n=0-4$ ;  $-CO-O-C_{2-4}alkenyl$ ;  $-CO-C_{1-4}alkyl$ ;  $-C_{1-4}alkylene-CONR^4R^5$  where  $R^4$  &  $R^5$  are independently selected from H,  $C_{1-4}alkyl$ .

Preferably  $R^2$  is selected from H and  $-CO-C_{1-4}alkyl$ .

Preferably L is selected from  $-CH_2-NR^{18}-$ ;  $-CH_2NR^{21}-T$ .

20 Preferably A is selected from phenyl, naphthyl, pyridyl and thienyl.

Preferably combinations of  $R^3$  and p are selected from:

- i)  $R^3$  is selected from a group of Formula II:  $-C_{1-4}alkylR^7$ ;  $-O-R^7$  and:  $R^7$ ; and  $p=1-3$  with the proviso that one value of  $R^3$  is a group of Formula II;
- ii)  $p=0$  with the proviso that A is naphthyl and L is  $-CH_2NR^{21}-T$ ;
- 25 iii)  $p=1$  with the proviso that  $R^3$  = a group of Formula II and A is naphthyl.

In another embodiment of the invention it is preferred that:

$R^1$  is selected from H;  $-C_{1-4}alkyl$ ,  $-C_{1-3}alkylene-Ph$  optionally mono or di-substituted on Ph with substituents selected from  $C_{1-4}alkyl$ , halogen, OH,  $C_{1-4}alkoxy$ ,  $C_{1-4}alkanoyl$ ,  $C_{1-4}alkanoyloxy$ , amino,  $C_{1-4}alkylamino$ , di( $C_{1-4}alkyl$ )amino,  $C_{1-4}alkanoylamino$ , thiol,  $C_{1-4}alkylthio$ , nitro, cyano, carboxy, carbamoyl,  $C_{1-4}alkoxycarbonyl$ ,  $C_{1-4}alkylsulfinyl$ ,  $C_{1-4}alkylsulfonyl$ , sulfonamido:  $-CO-C_{1-4}alkyl$ ;  $-CO-O-C_{1-4}alkyl$ ;

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SUBSTITUTE SHEET (RULE 26)

- 5 -

- CO-O-C<sub>2-4</sub>alkenyl; -CO-O-CH<sub>2</sub>-Ph optionally mono- or di-substituted on phenyl with substituents selected from C<sub>1-4</sub>alkyl, halogen, OH, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoyloxy, amino, C<sub>1-4</sub>alkylamino, di(C<sub>1-4</sub>alkyl)amino, C<sub>1-4</sub>alkanoylamino, thiol, C<sub>1-4</sub>alkylthio, nitro, cyano, carboxy, carbamoyl, C<sub>1-4</sub>alkoxycarbonyl, C<sub>1-4</sub>alkylthiono.
- 5 C<sub>1-4</sub>alkylsulfonyl, sulfonamido: -C<sub>1-4</sub>alkylene-CONR<sup>4</sup>R<sup>5</sup> where R<sup>4</sup> & R<sup>5</sup> are independently selected from H, C<sub>1-4</sub>alkyl; -C<sub>1-4</sub>alkylene-COOR<sup>6</sup> where R<sup>6</sup> is selected from H, C<sub>1-4</sub>alkyl;
- R<sup>2</sup> is selected from H; -C<sub>1-4</sub>alkyl; -C<sub>1-3</sub>alkylene-Ph; -COC<sub>1-4</sub>alkyl; -COOC<sub>1-4</sub>alkyl; R<sup>3</sup> is selected from H; OH; CN; CF<sub>3</sub>; NO<sub>2</sub>; -C<sub>1-4</sub>alkyl, -C<sub>1-4</sub>alkylene-R<sup>7</sup> where R<sup>7</sup> is
- 10 selected from phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 3 heteroatoms selected from O, N and S; C<sub>2-4</sub>alkenyl; halogen: -(CH<sub>2</sub>)<sub>n</sub>COOR<sup>8</sup> where n= 0-3 and R<sup>8</sup> represents H, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl; -CONR<sup>9</sup>R<sup>10</sup> where R<sup>9</sup> and R<sup>10</sup> independently represent H, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, -O-C<sub>1-4</sub>alkyl, -O-C<sub>2-4</sub>alkenyl;
- 15 -CON(R<sup>11</sup>)OR<sup>12</sup> where R<sup>11</sup> and R<sup>12</sup> independently represent H, C<sub>1-4</sub>alkyl and C<sub>2-4</sub>alkenyl; a group of Formula II, -CONR<sup>13</sup>-CHR<sup>14</sup>-COOR<sup>17</sup>, where R<sup>13</sup> is H or C<sub>1-4</sub>alkyl, R<sup>17</sup> is H or C<sub>1-6</sub>alkyl, R<sup>14</sup> is the side chain of a lipophilic amino acid with L or D configuration at the chiral alpha carbon in the corresponding free amino acid; C<sub>1-4</sub>alkyl monosubstituted on carbon with =N-OH; -SO-C<sub>1-4</sub>alkyl; -SO<sub>2</sub>-C<sub>1-4</sub>alkyl;
- 20 a group of Formula -X-R<sup>15</sup> where X is selected from CO, CH<sub>2</sub>, S, SO, SO<sub>2</sub> and R<sup>15</sup> is selected from C<sub>1-6</sub>alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 3 heteroatoms selected from O, N and S;
- p is 0-3 in which R<sup>3</sup> values can be the same or different;
- L is a linking moiety selected from the following groups written from left to right in
- 25 Formula I:
- CO-NR<sup>16</sup>- where R<sup>16</sup> is selected from H, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylene-Z and Z is selected from -O-C<sub>1-4</sub>alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 3 heteroatoms selected from O, N and S; -CH<sub>2</sub>-NR<sup>18</sup>- where R<sup>18</sup> represents any value defined for R<sup>16</sup>; -CH<sub>2</sub>S-; -CH<sub>2</sub>O-; -CH<sub>2</sub>-CHR<sup>19</sup>- where R<sup>19</sup> represents
- 30 any value defined for R<sup>16</sup>; -CH=CR<sup>20</sup>- where R<sup>20</sup> represents any value defined for R<sup>16</sup>; -CH<sub>2</sub>NR<sup>21</sup>-T- where R<sup>21</sup> represents any value defined for R<sup>16</sup>, T represents -(CH<sub>2</sub>)<sub>n</sub>- where

SUBSTITUTE SHEET (RULE 26)

- 6 -

n is 1-4 and T is optionally monosubstituted with  $R^{22}$  where  $R^{22}$  represents any value for  $R^{16}$  other than H. and provided at least one of  $R^{21}$  and  $R^{22}$  is H:  $-\text{CH}_2\text{NR}^{23}-\text{SO}_2-$  where  $R^{23}$  represents any value defined for  $R^{16}$ ;  $-\text{CH}_2\text{NR}^{24}-\text{CO}-\text{T}-$  where  $R^{24}$  represents any value defined for  $R^{16}$ . T represents  $-(\text{CH}_2)_n-$  where n is 0-4 and T is optionally monosubstituted with  $R^{29}$  where  $R^{29}$  represents any value for  $R^{16}$  other than H. and provided at least one of  $R^{24}$  and  $R^{29}$  is H;  $-\text{CO}-\text{NR}^{25}-\text{T}-$  where  $R^{25}$  represents any value defined for  $R^{16}$ . T represents  $-(\text{CH}_2)_n-$  where n is 1-4 and T is optionally monosubstituted with  $R^{26}$  where  $R^{26}$  represents any value for  $R^{16}$  other than H. and provided at least one of  $R^{24}$  and  $R^{25}$  is H;  $-\text{CH}_2\text{S}-\text{T}-$  where T represents  $-(\text{CH}_2)_n-$  where n is 1-4 and T is optionally monosubstituted with  $R^{27}$  where  $R^{27}$  represents any value for  $R^{16}$  other than H;  $-\text{CH}_2\text{O}-\text{T}-$  where T represents  $-(\text{CH}_2)_n-$  where n is 1-4 and T is optionally monosubstituted with  $R^{28}$  where  $R^{28}$  represents any value for  $R^{16}$  other than H:

A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 3 or 5 heteroatoms in the case of monocyclic and bicyclic rings respectively where the heteroatoms are independently selected from O, N & S; or a  $-\text{S}-\text{S}-$  dimer thereof when  $R^2=\text{H}$ .

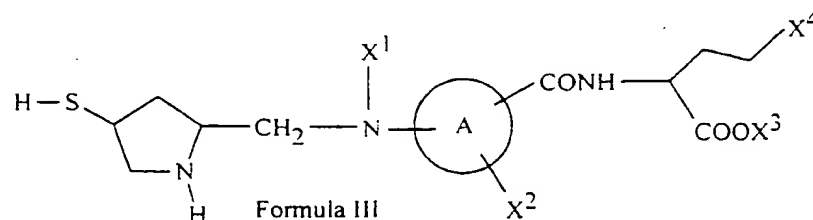
A preferred pharmaceutical composition is in the form of a tablet.

According to another aspect of the invention there is provided a compound of Formula I, III, IV or V for use as a medicament.

According to another aspect of the invention there is provided a compound of Formula I, III, IV or V for use in preparation of a medicament for treatment of a disease mediated through farnesylation of ras.

Many compounds of Formula I are a feature of this invention and in particular according to another aspect of the invention there is provided a compound of any of the following classes i), ii) or iii):

class i)



wherein:

**SUBSTITUTE SHEET (RULE 26)**



- 7 -

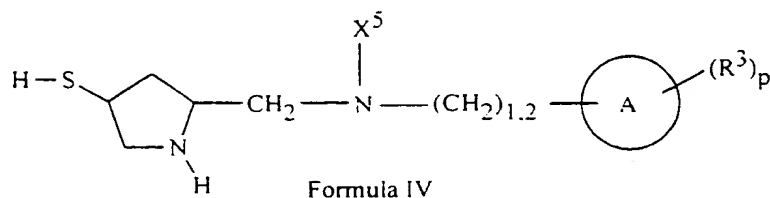
$X^1$  is selected from H;  $C_{1-6}$ alkyl; hydroxy $C_{1-6}$ alkyl;  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl;  $C_{1-6}$ alkylcarbonyl; hydroxy $C_{1-6}$ alkylcarbonyl;  $C_{1-6}$ alkoxy $C_{1-6}$ alkylcarbonyl;

A is selected from phenyl, naphthyl or a 5-10 membered heterocyclic ring having upto 5 heteroatoms selected from O, N and S;

- 5  $X^2$  is selected from H; phenyl; phenyl $C_{1-6}$ alkyl; a 5-6 membered heteroaryl ring containing upto 3 heteroatoms selected from O, N and S optionally linked to A by  $C_{1-6}$ alkyl; and  $X^2$  is optionally substituted on any ring as defined for phenyl in  $R^1 = -C_{1-3}$ alkylene-Ph in claim 1;

$X^3$  is selected from H;  $C_{1-6}$ alkyl;

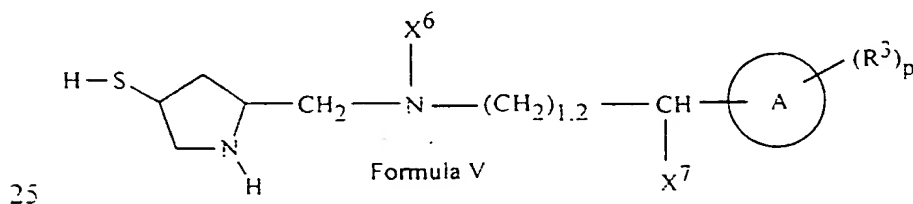
- 10  $X^4$  is selected from  $C_{1-6}$ alkylsulfanyl;  $C_{1-6}$ alkylsulfinyl;  $C_{1-6}$ alkylsulfonyl; carbamoyl;  $\underline{N}$ -( $C_{1-6}$ alkyl)carbamoyl;  $\underline{N}$ -(di $C_{1-6}$ alkyl)carbamoyl; and hydroxy or a  $C_{1-4}$ alkyl ether thereof: class ii)



wherein:

- 15  $X^5$  is selected from  $-CO-C_{1-4}$ alkyl-Ph;  $-CO-C_{1-6}$ alkyl;  $-CO-C_{1-4}$ alkyl-heteroaryl where heteroaryl is a 5-10 membered heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and Ph or heteroaryl are optionally substituted as defined for Ph in  $R^1 = -C_{1-3}$ alkylene-Ph;  $C_{1-4}$ alkyloxy $C_{1-4}$ alkyl;
- 20 A is naphthyl or a 10 membered heterocyclic ring having upto 5 heteroatoms selected from O, N and S;
- $R^3$  and p are as defined in claim 1;

class iii)



SUBSTITUTE SHEET (RULE 26)

- 8 -

wherein:

$X^6$  has any value defined for  $X^5$  in ii) above;

$X^7$  is Ph optionally substituted as defined for Ph in  $R^1 = -C_{1-3}\text{alkylene-Ph}$ ;

A is Ph or naphthyl or a 5-10 membered heterocyclic ring having upto 5 heteroatoms

5 selected from O, N and S;

$R^3$  and p are as defined above;

or a N-oxide, pharmaceutically acceptable salt, prodrug or solvate thereof.

Preferred values for compounds of class i) include.

$X^1$  is selected from H and  $C_{1-6}\text{alkoxy}C_{1-6}\text{alkyl}$ ;

10  $X^2$  is selected from H; phenyl or  $\text{phenyl}C_{1-6}\text{alkyl}$ ;

$X^4$  is  $C_{1-6}\text{alkylsulfanyl}$ ;

A is selected from phenyl or naphthyl;

Other preferred values for  $X^4$  are -OMe and the lactone which can be formed when  $X^4$  is OH and  $X^3$  is H.

15 Preferred values for compounds of class ii) include p is 0.

Preferred values for compounds of class iii) include.

$X^7$  is Ph;

A is Ph;

p is 0.

20 In another embodiment of the invention there is provided a compound of Formula I

in which:  $R^1$  is selected from H or  $C_{1-4}\text{alkyl}$ ;  $R^2$  is selected from H,  $C_{1-4}\text{alkyl}$ ,

$-\text{COC}_{1-4}\text{alkyl}$ ;  $-\text{C}_{1-4}\text{alkylPh}$ ; L is selected from the following values as defined herein.

$\text{CONR}^{16}$ ,  $\text{CH}_2\text{S}$ ,  $\text{CH}_2\text{O}$ ,  $\text{CH}_2\text{CHR}^{19}$ ,  $\text{CH}=\text{CHR}^{20}$ ,  $\text{CH}_2\text{NR}^{24}\text{COT}$ ,  $\text{CONR}^{25}\text{T}$ ,  $\text{CH}_2\text{ST}$  and

$\text{CH}_2\text{OT}$ ; and values for A,  $R^3$  and p are as defined herein, with the proviso that 2-

25 (benzylcarbamoyl)-4-sulfanylpyrrolidine and 4-(acetylsulfonyl)-2(benzylcarbamoyl)-pyrrolidine are excluded. It is believed that the excluded compounds were disclosed as intermediates for beta-lactam antibiotic synthesis in Japanese patent application 60233076 (Sumitomo Chemical).

According to another aspect of the present invention there is provided any one of  
30 the following individual compounds or a pharmaceutically acceptable salt thereof:

- (2S)-2-{2-Benzyl-5-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-benzoylamino}-4-methylsulfanylbutyric acid methyl ester :
- (2S)-2-{2-Benzyl-5-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-benzoylamino}-4-methylsulfanylbutyric acid :
- 5 (2S)-2-({2-phenyl-5-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester:
- (2S)-2-({2-phenyl-5-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid:
- (2S)-2-({3-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-naphthalene-1-carbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester :
- 10 (2S)-2-({3-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-naphthalene-1-carbonyl)-amino)-4-methylsulfanylbutyric acid :
- (2S)-2-({3-phenyl-5[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester:
- 15 (2S)-2-({3-phenyl-5[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid:
- (2S,4S)-2-{[N-(4-methoxybenzyl)-N-(naphthalen-1-ylmethyl)-amino]-methyl}-pyrrolidine-4-thiol :
- N-(naphthalen-1-ylmethyl)-N-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-pentanamide :
- 20 N-(naphthalen-1-ylmethyl)-N-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-2-(pyridin-3-yl)-acetamide :
- N-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-3-methyl-N-(2-naphthalen-1-yl-ethyl)butyramide :
- N-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl)-N-(2-naphthalen-1-yl-ethyl)-2-pyridin-3-yl-
- 25 acetamide ;
- (2S,4S)-2-{{(3-Methoxypropyl)-(2-naphthalen-1-ylethyl)amino}methyl}-pyrrolidine-4-thiol;
- N-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl)-2-(4-methoxy-phenyl)-N-(2-naphthalen-2-yl-ethyl)-acetamide :
- 30 (2S,4S)-2-{{(2-(4-Methoxyphenyl)ethyl)-(2-naphthalen-1-ylethyl)amino}methyl}-pyrrolidine-4-thiol ;

- 10 -

N-(2,2-Diphenyl-ethyl)-N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-butylamide :

N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-2-yl-ethyl)-butylamide :

- 5 N-(2,2-Diphenyl-ethyl)-N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-butylamide :

(2S)-2-{3-[(2S,4S]-4-Sulfanyl-pyrrolidin-2-ylmethyl)-(3-methoxy-propyl)-amino}-benzoylamino}-4-methylsulfanyl-butyl acid ;

N-([2S,4S]-4-Sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-1-yl-ethyl)-

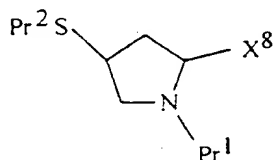
- 10 butylamide :

(2S)-4-Carbamoyl-2-({2-phenyl-5-[(2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-amino}-phenylcarbonyl)-amino)-butyl acid; and

(2S)-4-Carbamoyl-2-({2-phenyl-5-[(2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-amino}-phenylcarbonyl)-amino)-butyl acid methyl ester.

- 15 According to another aspect of the invention there is provided a pharmaceutical composition comprising a compound as defined in any one Formulas III, IV or V or an individual compound listed above together with a pharmaceutically acceptable diluent or carrier.

- According to another aspect of the invention there is provided a process for  
20 preparing compounds of classes i), ii) or iii) as defined above which comprises deprotecting a compound of Formula VI



Formula VI

- wherein X<sup>8</sup> represents the right hand side of compound classes i), ii) or iii) as defined above. Pr<sup>1</sup> is H or an amino protecting group, Pr<sup>2</sup> is H or a thio protecting group and any  
25 functional groups in X<sup>8</sup> are optionally protected with the proviso that there is at least one protecting group and optionally, if desired, converting the product thus obtained into a pharmaceutically acceptable salt thereof.

In an embodiment of the invention:

**SUBSTITUTE SHEET (RULE 26)**

- 11 -

Examples of values for  $R^1$  include methyl:  $-\text{CH}_2\text{-Ph}$ ;  $-\text{CH}_2\text{-Ph}$  substituted on Ph with nitro, especially 4-nitro; acetyl: BOC; allyloxycarbonyl:  $-\text{CO-O-CH}_2\text{-Ph}$  substituted on Ph with nitro, especially 4-nitro:  $-\text{CH}_2\text{CONH}_2$ .

Examples of values for  $R^2$  include  $-\text{COMe}$  and  $-\text{COO}i\text{tertbutyl}$ .

5 Examples of values for  $R^3$  include Cl:  $-\text{COOH}$ ;  $-\text{CONH}_2$ ;  $-\text{SOMe}$  and;  $-\text{SO}_2\text{Me}$ .

When  $R^3$  represents  $-(\text{CH}_2)_n\text{-COOR}^8$  a suitable value for  $n$  is 0.

Examples of lipophilic amino acids which contribute their side chain (denoted  $R^{14}$  within the definition of values for  $R^3$ ) include methionine, phenylglycine, phenylalanine, serine, leucine, isoleucine or valine.  $L$  configuration in the corresponding free amino acid  
10 is preferred. Examples of amino acid side chains are set out below. A preferred value for  $R^{14}$  is  $-\text{CH}_2\text{-CH}_2\text{-S-CH}_3$ . Further preferred values for  $R^{14}$  are  $-\text{CH}_2\text{-OMe}$  and  $-\text{CH}_2\text{-CH}_2\text{-OMe}$ .

When  $R^{17}$  is H to give a  $\text{COOH}$  group in Formula II, and  $R^{14}$  is  $-\text{CH}_2\text{-CH}_2\text{-OH}$  then a lactone can be formed where  $R^{17}$  and  $R^{14}$  together form part of a dihydrofuran-2-one  
15 heterocyclic ring. The same lactone can be formed for compounds of Formula III where  $X^4$  is OH and  $X^3$  is H.

Amino Acid	Side Chain
methionine	$-\text{CH}_2\text{-CH}_2\text{-S-CH}_3$
phenylglycine	Ph
phenylalanine	$-\text{CH}_2\text{-Ph}$
serine	$-\text{CH}_2\text{OH}$ or a $\text{C}_{1-4}$ alkyl (preferably methyl) ether thereof.
leucine	$-\text{CH}_2\text{-CHMe}_2$
homoserine	$-\text{CH}_2\text{-CH}_2\text{-OH}$ or a $\text{C}_{1-4}$ alkyl (preferably methyl) ether thereof.

20 A preferred value for  $p$  is 2.

When  $L$  is  $-\text{CH}_2\text{NR}^{21}\text{-T}$  a suitable value for  $n$  is 1. When  $L$  is  $-\text{CH}_2\text{NR}^{24}\text{-CO-T}$  a suitable value for  $n$  is 1. When  $L$  is  $-\text{CH}_2\text{NR}^{25}\text{-T}$  a suitable value for  $n$  is 1. When  $L$  is  $-\text{CH}_2\text{-S-T}$  a suitable value for  $n$  is 1. When  $L$  is  $-\text{CH}_2\text{-O-T}$  a suitable value for  $n$  is 1.  $L$  is especially  $-\text{CONH-}$ ,  $-\text{CH}_2\text{-NH-}$ ,  $-\text{CH}_2\text{NHSO}_2\text{-}$ ,  $-\text{CH}_2\text{NHCO-}$ .

SUBSTITUTE SHEET (RULE 26)

- 12 -

Examples of values for A when A is heteroaryl are thienyl, pyridyl, quinolyl & quinoxaliny.

Further preferred values are set out below.

For R<sup>1</sup>: 4-nitro-benzyloxycarbonyl; allyloxycarbonyl; carbamoylmethyl; acetyl;

5 phenoxycarbonyl; H.

For R<sup>2</sup>: Acetylsulfanyl; H.

For R<sup>3</sup>: Methoxycarbonyl; N-methyl-N-methoxy-carbamoyl; nitro; allyloxycarbonyl;

N-methyl-allyloxycarbamoyl; ethoxycarbonyl; 3,4-dichloro-benzyl-carbamoyl; hydroxy; carboxy; (2S),4-methylsulfanyl-butyric acid methyl ester-2yl-carbamoyl;

10 (2S),4-methylsulfanyl-butyric acid-2yl-carbamoyl; phenoxy.

For p: 1-2, especially 2; a further preferred value is 0.

For L: -C(O)-NH-; -CH<sub>2</sub>-C(O)-NH-; -CH<sub>2</sub>-NH-C(O)-; -CH<sub>2</sub>-NH-SO<sub>2</sub>-; especially -C(O)-NH-.

For A: phenyl; pyridyl, thienyl; naphthyl.

15 For R<sup>16</sup> & R<sup>18-26</sup>: H, C<sub>1-4</sub>alkyl, especially H.

In another embodiment of the invention preferred values are set out below.

In compounds of Formula III: X<sup>1</sup> is H or methoxyC<sub>1-4</sub>alkyl (especially H); X<sup>2</sup> is H, phenyl or benzyl (especially benzyl); X<sup>3</sup> is H or C<sub>1-4</sub>alkyl (especially H); X<sup>4</sup> is

C<sub>1-4</sub>alkylsulfanyl (especially methylsulfanyl); and A is phenyl. When A is a 6-membered

20 aryl or heteroaryl ring then groups -NX<sup>1</sup>- and the substituent comprising X<sup>4</sup> are preferably in meta juxtaposition relative to each other; and X<sup>2</sup>, if present, is preferably positioned para relative to -NX<sup>1</sup>-. The chiral carbon to which -COOX<sup>3</sup> is attached is preferably in S configuration. The chiral carbons at the 2 and 4 positions of the pyrrolidine ring are preferably in S configuration.

25 In compounds of Formula IV: X<sup>5</sup> is -CO-C<sub>1-4</sub>alkyl (especially -CO-CH<sub>2</sub>-CHMe<sub>2</sub>) or -CH<sub>2</sub>-Ph-O-C<sub>1-4</sub>alkyl (especially -CH<sub>2</sub>-Ph-OMe); heteroaryl is preferably pyridyl and a preferred aryl or heteroaryl substituent is -O-C<sub>1-4</sub>alkyl (especially methoxy); and A is naphthyl. The chiral carbons at the 2 and 4 positions of the pyrrolidine ring are preferably in S configuration. The attachment point for A relative to -(CH<sub>2</sub>)<sub>1,2</sub>- is preferably at the 1

30 position of naphthalene and the equivalent position for heterocyclic values for A

- 13 -

(regardless of ring numbering conventions for heterocycles). A preferred value for  $-(CH_2)_{1,2}-$  is  $-(CH_2)_2-$ .

In compounds of Formula V:  $X^6$  is  $-CO-C_{1-5}alkyl$  (more preferably  $-CO-CH_2-CHMe_2$  or  $-CO-CH_2-t-butyl$ , especially  $-CO-CH_2-CHMe_2$ ) or  $-CH_2-Ph-O-C_{1-4}alkyl$  (especially  $-CH_2-Ph-OMe$ ); heteroaryl is preferably pyridyl and a preferred aryl substitution is  $-O-C_{1-4}alkyl$  (especially methoxy); and A is phenyl or naphthyl (especially phenyl). The chiral carbons at the 2 and 4 positions of the pyrrolidine ring are preferably in S configuration. A preferred value for  $-(CH_2)_{1,2}-$  is  $-(CH_2)_1-$ .

Suitable pairs of values for  $R^3$  when  $p=2$  are:  $-COOMe$ ,  $-CO.N(Me).OMe$ ;  $NO_2$ ,  $-CO.N(Me).OMe$ ;  $-COOMe$ , allyloxycarbonyl;  $-CO.N(Me).OMe$ , allyloxycarbonyl; allyloxycarbonyl,  $-CO.N(Me).O.CH_2CH=CH_2$ ;  $OH$ ,  $COOH$ ;  $-COOMe$ ,  $COOMe$ ;  $Ph$ ,  $-CO.N-Methionine$  methyl ester;  $Ph$ ,  $-CO.N-Methionine$ ; benzyl,  $-CO.N-Methionine$  methyl ester; benzyl,  $-CO.N-Methionine$ ; benzyl,  $-CO.N-Methionine$  isopropyl ester;  $Ph$ ,  $-CO.N\alpha-Glutamine$  methyl ester;  $Ph$ ,  $-CO.N\alpha-Glutamine$ .

Suitable values for  $L = CHNR^{21}T$  include  $CH_2.N(CO.CH_2.CHMe_2).CH_2.CH_2$ ;  $CH_2.N(CH_2.CH_2.CH_2OMe).CH_2.CH_2$ ;  $CH_2.N(CH_2.pPh.OMe).CH_2.CH_2$ ;  $CH_2.N(CO.CH_2.CHMe_2).CH_2$ ;  $CH_2N(CO.CH_2.CH_2.CH_2.Me).CH_2$ ;  $CH_2N(CO.CH_2.CHMe.CH_2Me).CH_2$ ;  $CH_2N(CO.CH_2.CH_2.OMe)CH_2$ ;  $CH_2N(CO.CH_2.pyridin-3-yl).CH_2$ ;  $CH_2N(4-methoxybenzyl)CH_2$ ;  $CH_2N(CO.CH_2.CHMe_2)CH_2.CH_2.CH(Ph)$ ;  $CH_2N(CO.CH_3)CH_2.CH_2.CH(Ph)$ ;  $CH_2N(CO.CH_2.CHMe_2)CH_2$ ;  $CH_2N(CO.CH_3)CH_2$ ;  $CH_2N(CO.CH_2.CHMe_2)CH_2.CH(Ph)$ ;  $CH_2N(CO.CH_2.CMe_3)CH_2.CH(Ph)$ ;  $CH_2N(CO.CH_2.pyridin-3-yl)CH_2.CH(Ph)$ ;  $CH_2N(CO.1-hydroxy-6-methoxy-pyridin-3-yl)CH_2.CH(Ph)$ ;  $CH_2N(CO.CH_2.CHMe_2)CH_2.CH_2$ ;  $CH_2N(CO.CH_2.CMe_3)CH_2.CH_2$ ;  $CH_2N(CO.CH_2.pyridin-3-yl)CH_2.CH_2$ ;  $CH_2N(CO.4-methoxybenzyl)CH_2.CH_2$ ;

Suitable values for  $L = -CH_2NR^{18}-$  include  $CH_2NH$ ;  $CH_2NMe$ ;  $CH_2N(CO.CH_2.CHMe_2)$  and  $CH_2N(CO.CH_2.CH_2.OMe)$ .

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard
- 5 p. 113-191 (1991);
- c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

Examples of pro-drugs include *in vivo* hydrolysable esters of a compound of the

10 Formula I. An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid. Suitable pharmaceutically-acceptable esters for carboxy include C<sub>1-6</sub>alkoxymethyl esters for example methoxymethyl, C<sub>1-6</sub>alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C<sub>3-</sub>

15 <sub>8</sub>cycloalkoxycarbonyloxyC<sub>1-6</sub>alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C<sub>1-</sub><sub>6</sub>alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Particular substitutions on A for 6 membered rings are in the meta or para

20 positions.

Some compounds within the scope of Formula I are known as intermediates in carbapenem side chain synthesis but it is believed that they have not been previously described in forms suitable as pharmaceutical compositions nor had any pharmaceutical activity associated with them *per se*. The reader is referred to the following publications in

25 this regard and also in respect of synthetic details for compound preparation: Matsumura, Heterocycles (1995), 41, 147-59; European patent application EP 590885 (Zeneca; Betts *et al.*); European patent application EP 592167 (Zeneca; Siret); European patent application EP 562855 (Zeneca; Jung *et al.*); International patent application WO 92/17480 (Imperial Chemical Industries; Betts *et al.*); European patent application EP 508682 (Imperial

30 Chemical Industries; Betts *et al.*); European Patent Application EP 280771 (Fujisawa Pharmaceutical, Murata *et al.*); and International patent application WO 92/17479 (Imperial



Chemical Industries: Betts *et al*).

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only and references to individual  
5 branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. An analogous convention applies to other generic terms.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active  
10 or racemic form which possesses the property of inhibiting FTPase. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, inhibitory properties against FTPase may be evaluated using the standard laboratory techniques referred to hereinafter.

15 The term " halogen " refers to fluorine, chlorine, bromine and iodine. The term " carbamoyl " refers to  $-C(O)NH_2$ . The term " BOC " refers to *tert*-butyl-O-C(O)-. The term " allyl " refers to  $CH_2=CH-CH_2-$ . Bicyclic aryl and bicyclic heteroaryl rings refer to ring systems in which both rings of the bicyclic system are aromatic.

Examples of **C<sub>1-6</sub>alkyl** include methyl, ethyl, propyl, isopropyl, *sec*-butyl, *tert*-butyl  
20 and pentyl; examples of **C<sub>1-4</sub>alkyl** include methyl, ethyl, propyl, isopropyl, *sec*-butyl and *tert*-butyl; examples of **C<sub>1-3</sub>alkyl** include methyl, ethyl, propyl and isopropyl; examples of **-C<sub>1-3</sub>alkylenePh** include benzyl, phenylethyl, phenylpropyl; examples of **C<sub>1-4</sub>alkoxy** (also called **-O-C<sub>1-4</sub>alkyl** herein) include methoxy, ethoxy and propoxy; examples of **C<sub>1-4</sub>alkanoyl** include formyl, acetyl and propionyl; examples of **C<sub>1-4</sub>alkanoyloxy**  
25 include acetyloxy and propionyloxy; examples of **C<sub>1-4</sub>alkylamino** include methylamino, ethylamino, propylamino, isopropylamino, *sec*-butylamino and *tert*-butylamino; examples of **di-(C<sub>1-4</sub>alkyl)amino** include di-methylamino, di-ethylamino and *N*-ethyl-*N*-methylamino; examples of **C<sub>1-4</sub>alkanoylamino** include acetamido and propionylamino; examples of **C<sub>1-4</sub>alkoxycarbonyl** include methoxycarbonyl, ethoxycarbonyl and  
30 propoxycarbonyl; examples of **C<sub>1-4</sub>alkylsulfanyl** include methylsulfanyl, ethylsulfanyl, propylsulfanyl, isopropylsulfanyl, *sec*-butylsulfanyl and *tert*-butylsulfanyl; examples of

- 16 -

- C<sub>1-4</sub>alkylsulfinyl** include methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, *sec*-butylsulfinyl and *tert*-butylsulfinyl; examples of **C<sub>1-4</sub>alkylsulfonyl** include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, *sec*-butylsulfonyl and *tert*-butylsulfonyl; examples of **-CO-C<sub>1-4</sub>alkyl** include formyl, acetyl, propionyl, butyryl, and valeryl; examples of **-CO-O-C<sub>1-4</sub>alkyl** include ethyloxycarbonyl; propyloxycarbonyl and *tert*-butoxycarbonyl (BOC);
- examples of **-CO-O-C<sub>2-4</sub>alkenyl** include allyloxycarbonyl and vinyloxycarbonyl; examples of **-CO-O-(CH<sub>2</sub>)<sub>n</sub>Ph** where n=0-4 include phenyloxycarbonyl, benzyloxycarbonyl, phenylethyloxycarbonyl and phenylpropyloxycarbonyl;
- 10 examples of **-C<sub>1-4</sub>alkylene-CONR<sup>4</sup>R<sup>5</sup>** include carbamoylmethyl, carbamoylethyl, N-methylcarbamoylethyl, N-methyl-N-ethylcarbamoylethyl; examples of **-C<sub>1-4</sub>alkylene-COOR<sup>6</sup>** include carboxymethyl, carboxyethyl, carboxypropyl, propionic acid methyl ester, acetic acid ethyl ester; examples of **C<sub>2-4</sub>alkenyl** include allyl and vinyl; examples of **-O-C<sub>2-4</sub>alkenyl** include allyloxy and vinyloxy; examples of **lipophilic amino**
- 15 **acids** include valine, leucine, isoleucine, methionine, phenylalanine, serine, threonine and tyrosine; examples of **carbamoylC<sub>1-4</sub>alkyl** include carbamoylmethyl, carbamoylethyl and carbamoylpropyl; examples of **N-(monoC<sub>1-4</sub>alkyl)carbamoylC<sub>1-4</sub>alkyl** include N-methylcarbamoylmethyl and N-ethylcarbamoylethyl; examples of **N-(diC<sub>1-4</sub>alkyl)carbamoylC<sub>1-4</sub>alkyl** include N,N-dimethylcarbamoylethyl and N-methyl-N-ethylcarbamoylethyl;
- 20 examples of **C<sub>1-4</sub>alkyl monosubstituted on carbon with =N-OH** include butyraldehyde oxime and propionaldehyde oxime; examples of **hydroxyC<sub>1-6</sub>alkyl** include hydroxymethyl, hydroxyethyl, hydroxypropyl, 2-hydroxypropyl, 2-(hydroxymethyl)propyl and hydroxypentyl; examples of **C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl** include methoxyethyl, ethoxyethyl and methoxybutyl; examples of **C<sub>1-6</sub>alkylcarbonyl** include methylcarbonyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, *sec*-butylcarbonyl, *tert*-butylcarbonyl and
- 25 **pentylcarbonyl**; examples of **hydroxyC<sub>1-6</sub>alkylcarbonyl** include hydroxyacetyl, hydroxypropionyl, hydroxybutyryl, 3-hydroxybutyryl and hydroxypentanoyl; examples of **C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkylcarbonyl** include methoxyacetyl, methoxypropionyl, ethoxybutyryl and butoxyacetyl; examples of **phenylC<sub>1-6</sub>alkyl** include benzyl, phenylethyl and
- 30 **phenylpropyl**; examples of **-CO-C<sub>1-4</sub>alkyl-Ph** include phenylacetyl and phenylpropionyl; examples of **-CO-C<sub>1-4</sub>alkyl-heteroaryl** include 2-(3-pyridyl)-acetyl and 2-(3-thienyl)-

SUBSTITUTE SHEET (RULE 26)

- 17 -

acetyl: examples of N-(C<sub>1-6</sub>alkyl)carbamoyl include N-methyl-carbamoyl and N-ethyl-carbamoyl: examples of N-(diC<sub>1-6</sub>alkyl)carbamoyl include N,N-dimethylcarbamoyl and N-methyl-N-ethylcarbamoyl.

Examples of **5-10 membered monocyclic or bicyclic heteroaryl rings containing upto 5 heteroatoms selected from O,N and S** include the following.

Examples of 5- or 6-membered heteroaryl ring systems include imidazole, triazole, pyrazine, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole and thiophene. A 9 or 10 membered bicyclic heteroaryl ring system is an aromatic bicyclic ring system comprising a 6-membered ring fused to either a 5 membered ring or another 6 membered ring. Examples of 5/6 and 6/6 bicyclic ring systems include benzofuran, benzimidazole, benzthiophene, benzthiazole, benzisothiazole, benzoxazole, benzisoxazole, pyridoimidazole, pyrimidoimidazole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline and naphthyridine.

Preferably monocyclic heteroaryl rings contain upto 3 heteroatoms and bicyclic heteroaryl rings contain upto 5 heteroatoms. Preferred heteroatoms are N and S, especially N. In general, attachment of heterocyclic rings to other groups is via carbon atoms. Suitable values of heterocycles containing only N as the heteroatom are pyrrole, pyridine, indole, quinoline, isoquinoline, imidazole, pyrazine, pyrimidine, purine and pteridine.

Preferably any chiral carbon atoms at the 2 and 4 positions of the pyrrolidine ring in Formulas I and III-V are in S configuration.

Compounds of Formula I and III-V may form salts which are within the ambit of the invention. Pharmaceutically acceptable salts are preferred although other salts may be useful in, for example, isolating or purifying compounds.

When the compound contains a basic moiety it may form pharmaceutically acceptable salts with a variety of inorganic or organic acids, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. A suitable pharmaceutically-acceptable salt of the invention when the compound contains an acidic moiety is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a pharmaceutically-acceptable cation, for example a salt with

- 18 -

methyllamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Solvates, for example hydrates, are also within the ambit of the invention and may be prepared by generally known methods.

5           According to another aspect of the present invention there is provided a compound of Formula I for use as a medicament.

          According to another aspect of the present invention there is provided the use of a compound of Formula I in preparation of a medicament for treating ras mediated diseases, especially cancer.

10           According to another aspect of the present invention there is provided a method of treating ras mediated diseases, especially cancer, by administering an effective amount of a compound of Formula I to a mammal in need of such treatment.

          According to a further feature of the invention there is provided a compound of Formula I, or a pharmaceutically-acceptable salt thereof, for use in a method of  
15 treatment of the human or animal body by therapy.

          The invention also includes a method of treating a disease or medical condition mediated alone or in part by farnesylated ras which comprises administering to a mammal requiring such treatment an effective amount of an active ingredient as defined above. The invention also provides the use of such an active ingredient in the production  
20 of a new medicament for use in a farnesylated ras mediated disease or medical condition.

          Specific cancers of interest include:

- carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin;
- hematopoietic tumors of lymphoid lineage, including acute lymphocytic  
25 leukemia, B-cell lymphoma and Burketts lymphoma;
- hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia;
- tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; and
- 30 - other tumors, including melanoma, seminoma, tetratocarcinoma, neuroblastoma and glioma.

**SUBSTITUTE SHEET (RULE 26)**

- 19 -

The compounds of Formula I are especially useful in treatment of tumors having a high incidence of ras mutation, such as colon, lung, and pancreatic tumors. By the administration of a composition having one (or a combination) of the compounds of this invention, development of tumors in a mammalian host is reduced.

5        Compounds of Formula I may also be useful in the treatment of diseases other than cancer that may be associated with signal transduction pathways operating through Ras, e.g., neuro-fibromatosis.

      Compounds of Formula I may also be useful in the treatment of diseases associated with CAAX-containing proteins other than Ras (e.g., nuclear lamins and  
10 transducin) that are also post-translationally modified by the enzyme farnesyl protein transferase.

      The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams,  
15 ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

20        The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

      Suitable pharmaceutically acceptable excipients for a tablet formulation include,  
25 for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to  
30 modify their disintegration and the subsequent absorption of the active ingredient within

- 20 -

the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a

**SUBSTITUTE SHEET (RULE 26)**

- 21 -

dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

5           The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an  
10 esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol,  
15 propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents,  
20 which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the  
25 rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure  
30 well known in the art.

SUBSTITUTE SHEET (RULE 26)

- 22 -

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30 $\mu$  or much less. the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then  
5 conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an  
10 aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of  
15 Editorial Board). Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active  
20 agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch;  
25 Chairman of Editorial Board). Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the Formula I are  
30 useful in treating diseases or medical conditions which are due alone or in part to the effects of farnesylation of ras.

SUBSTITUTE SHEET (RULE 26)



- 23 -

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for  
5 intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

Compounds of this invention may be useful in combination with known  
10 anti-cancer and cytotoxic agents. If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

Although the compounds of the Formula I are primarily of value as therapeutic  
15 agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of activation of ras by farnesylation. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

According to another aspect of the present invention there is provided  
20 individual compounds produced as end products in the Examples set out below and salts thereof.

A compound of the invention, or a salt thereof, may be prepared by any process known to be applicable to the preparation of such compounds or structurally related compounds. Such processes are illustrated by the following representative schemes  
25 in which variable groups have any of the meanings defined for Formula I unless stated otherwise. Functional groups may be protected and deprotected using conventional methods. For examples of protecting groups such as amino and carboxylic acid protecting groups (as well as means of formation and eventual deprotection), see T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Second Edition, John  
30 Wiley & Sons, New York, 1991. Note abbreviations used have been listed immediately before the Examples below.

Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

5           Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not  
10 specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms).

Examples of carboxy protecting groups include straight or branched chain  
15 (1-12C)alkyl groups (e.g. isopropyl, *t*-butyl); lower alkoxy lower alkyl groups (e.g. methoxymethyl, ethoxymethyl, isobutoxymethyl; lower aliphatic acyloxy lower alkyl groups, (e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (e.g. 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (e.g. *p*-methoxybenzyl, *o*-nitrobenzyl,  
20 *p*-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (e.g. trimethylsilyl and *t*-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (e.g. trimethylsilylethyl); and (2-6C)alkenyl groups (e.g. allyl and vinylethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, metal- or enzymically-catalysed hydrolysis.

25           Examples of hydroxy protecting groups include lower alkenyl groups (e.g. allyl); lower alkanoyl groups (e.g. acetyl); lower alkoxycarbonyl groups (e.g. *t*-butoxycarbonyl); lower alkenyloxycarbonyl groups (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzoyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *o*-nitrobenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl); tri lower alkyl/arylsilyl groups (e.g. trimethylsilyl,  
30 *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl); aryl lower alkyl groups (e.g. benzyl) groups; and triaryl lower alkyl groups (e.g. triphenylmethyl).

Examples of amino protecting groups include formyl, aralkyl groups (e.g. benzyl and substituted benzyl, e.g. p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (e.g. t-butoxycarbonyl); lower alkenyloxycarbonyl (e.g. allyloxycarbonyl); aryl lower  
5 alkoxycarbonyl groups (e.g. benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); trialkylsilyl (e.g. trimethylsilyl and t-butyltrimethylsilyl); alkylidene (e.g. methylenedioxy); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include.  
10 for example, acid-, base, metal- or enzymically-catalysed hydrolysis, or photolytically for groups such as o-nitrobenzyloxycarbonyl, or with fluoride ions for silyl groups.

Examples of protecting groups for amide groups include aralkoxymethyl (e.g., benzyloxymethyl and substituted benzyloxymethyl); alkoxymethyl (e.g. methoxymethyl and trimethylsilylethoxymethyl); tri alkyl/arylsilyl (e.g. trimethylsilyl, t-butyltrimethylsilyl, t-butyl-  
15 butyldiphenylsilyl); tri alkyl/arylsilyloxymethyl (e.g. t-butyltrimethylsilyloxymethyl, t-butyl-  
butyldiphenylsilyloxymethyl); 4-alkoxyphenyl (e.g. 4-methoxyphenyl); 2,4-di(alkoxy)phenyl (e.g. 2,4-dimethoxyphenyl); 4-alkoxybenzyl (e.g. 4-methoxybenzyl); 2,4-di(alkoxy)benzyl (e.g. 2,4-di(methoxy)benzyl); and alk-1-enyl (e.g. allyl, but-1-enyl and substituted vinyl e.g. 2-phenylvinyl).

20 Aralkoxymethyl, groups may be introduced onto the amide group by reacting the latter group with the appropriate aralkoxymethyl chloride, and removed by catalytic hydrogenation. Alkoxymethyl, tri alkyl/arylsilyl and tri alkyl/silyloxymethyl groups may be introduced by reacting the amide with the appropriate chloride and removing with acid; or in the case of the silyl containing groups, fluoride ions. The alkoxyphenyl and alkoxybenzyl  
25 groups are conveniently introduced by arylation or alkylation with an appropriate halide and removed by oxidation with ceric ammonium nitrate. Finally alk-1-enyl groups may be introduced by reacting the amide with the appropriate aldehyde and removed with acid.

Compounds of Formula I in which L represents  $-\text{CO}-\text{NR}^{16}-$  may be prepared by forming an amide bond between compounds 1 and 2 as outlined in Scheme 23.

30 Compounds of Formula I in which L represents  $-\text{CO}-\text{NR}^{25}-\text{T}-$  may be prepared by an analogous procedure. Suitable coupling conditions include the following.

**SUBSTITUTE SHEET (RULE 26)**

- 26 -

- i) Use of EEDQ at room temperature in an organic solvent (e.g. dichloromethane, methanol).
- ii) Use of oxalyl chloride in an organic solvent (e.g. DMF,  $\text{CH}_2\text{Cl}_2$ ) in the presence of an organic base (e.g. NMM, triethylamine, DMAP) at  $0^\circ$  to room temperature  
5 for 0.5-16h.
- iii) Use of EDC/ HOBT in an organic solvent (e.g. DMF,  $\text{CH}_2\text{Cl}_2$ ).
- iv) Use of DCCI/ HOBT in an organic solvent (e.g. DMF,  $\text{CH}_2\text{Cl}_2$ ) in the presence of an organic base (e.g. triethylamine).
- v) Use of mixed anhydride reactions under standard conditions, for example  
10 isopropylchloroformate in an organic solvent (e.g. DMF, DMA, dichloromethane) in the presence of an organic base (e.g. NMM, DMAP, triethylamine).
- vi) Via an active ester under standard conditions e.g. pentafluorophenyl ester in an organic solvent (e.g. dichloromethane) in the presence of an organic base (e.g. triethylamine).
- 15 vii) Via an acid chloride under standard conditions e.g. using thionyl chloride and heat for about 150min followed by an organic base (e.g. triethylamine) in the presence of an organic solvent (e.g. acetonitrile).

Compounds of Formula I in which L represents  $-\text{CH}_2\text{NR}^{18}-$ ,  $-\text{CH}_2\text{O}-$  or  $-\text{CH}_2\text{S}-$  may be prepared as outlined in Scheme 24. LG represents a leaving group (e.g. mesyloxy, tosyloxy, halogen) and X represents S, O or  $\text{NR}^{18}$ . Suitable coupling conditions include the following.

- i) Use of an inorganic base (e.g.  $\text{NaHCO}_3$ , NaH,  $\text{K}_2\text{CO}_3$ , butyllithium) in an organic solvent (e.g. THF, DMF, DMSO) and a temperature of about  $70^\circ$  to  $150^\circ$
- ii) Use of an organic base (e.g. triethylamine, DMAP) in an organic solvent (e.g. THF, dichloromethane, DMA, DMF) at a temperature range of room temperature -  $150^\circ$
- 25 iii) Use of an inorganic base (e.g. KOH, NaOH,  $\text{K}_2\text{CO}_3$ ) in an aqueous (e.g. water) and organic solvents (e.g. dichloromethane) in a 2 phase system, optionally in the presence of a phase transfer catalyst (e.g. tetrabutylammoniumbromide).

Compounds of Formula I in which L represents  $-\text{CH}=\text{CR}^{20}-$  may be prepared  
30 using a Wittig reaction as outlined in Scheme 25. Suitable reaction conditions include the following.

**SUBSTITUTE SHEET (RULE 26)**

- 27 -

i) Use of a base (e.g. potassium carbonate, metal hydride, metal alkoxide) in the presence of an organic solvent (e.g. THF, toluene, DMSO) optionally in the presence of an aqueous solvent (2-phase system) and optionally in the presence of a catalyst complexing agent which solubilises alkali metal ions in non-polar solvents such as

- 5 1.4.7.10.13-pentaoxacyclopentadecane (also called 15-Crown-5) or  
1.4.7.10.13.16-hexaoxacyclooctadecane (also called 18-Crown-6).

Compounds of Formula I in which L represents  $-\text{CH}_2\text{NR}^{18}-$  may be prepared as outlined in Scheme 26 by coupling aldehyde (2) with compound 4. Suitable coupling conditions include the following.

- 10 i) Use of a reducing agent (e.g.  $\text{NaCNBH}_3$ ,  $\text{BH}_3$ , hydrogen plus catalyst,  $\text{LiHBEt}_3$ , di-isobutyl-aluminiumhydride, lithium aluminium hydride, sodium borohydride) in the presence of a suitable solvent e.g. ethanol & acetic acid.

Aldehyde (2) may be prepared by oxidation of the corresponding alcohol (1) under suitable conditions such as use of an oxidising agent (e.g. TPAP, NMM-O) in the  
15 presence of an organic solvent (e.g. acetonitrile, dichloromethane) at room temperature. Other suitable oxidising agents include chromium oxide, pyridinium chlorochromate, pyridinium dichromate, sodium dichromate and sodium hypochlorite.

Aldehyde (2) may also be prepared by reduction of the corresponding ester (1) under standard conditions using for example diisobutyl-aluminium hydride.

- 20 Compounds of Formula I in which L represents  $-\text{CH}_2\text{NR}^{21}\text{-T-}$ ,  $-\text{CH}_2\text{O-T-}$  or  $-\text{CH}_2\text{S-T-}$  may be prepared as outlined in Scheme 27 in which LG represents a leaving group (e.g. mesyloxy, tosyloxy, halogen) and X represents O, S or  $\text{NR}^{21}$ . Suitable coupling conditions are as outlined above in relation to Scheme 24. Optionally the positions of LG and XH in compounds 1 & 2 in Scheme 27 can be reversed to give the same end product.

- 25 Compounds of Formula I in which L represents  $-\text{CH}_2\text{NR}^{23}\text{-SO}_2-$  may be prepared as outlined in Scheme 28. Compounds 1 & 2 may be coupled under standard conditions such as the following.

- i) Use of an organic base (e.g. di-isopropyl-ethylamine, triethylamine, 4-methyl-morpholine) in the presence of an organic solvent (e.g. dichloromethane) at a  
30 temperature range of  $0^\circ - 40^\circ$

- 28 -

ii) Use of an inorganic base (e.g. potassium carbonate) in the presence of an organic solvent (e.g. DMF) at a temperature range of 0°-150°

Compounds of Formula I in which L represents  $-\text{CH}_2\text{-NR}^{24}\text{-CO-T-}$  may be prepared as outlined in Scheme 29. Compounds 1 & 2 may be coupled under standard conditions such as described above for  $\text{L} = -\text{CO-NR}^{16}-$ .

Compounds of Formula I in which L represents  $-\text{CH}_2\text{-CHR}^{19}-$  may be prepared as by reduction of compounds of the type set out as compound 3 in Scheme 25 but substituting  $\text{R}^{19}$  in lieu of  $\text{R}^{20}$ . Reduction is carried out under standard conditions with standard reagents for example using hydrogenation in the presence of a catalyst such as palladium on charcoal at room temperature.

Biological activity was tested as follows. Farnesyl protein transferase (FPT) was partially purified from human placenta by ammonium sulphate fractionation followed by a single Q-Sepharose<sup>®</sup> (Pharmacia, Inc) anion exchange chromatography essentially as described by Ray and Lopez-Belmonte (Ray K P and Lopez-Belmonte J (1992) Biochemical Society Transactions 20 494-497). The substrate for FPT was Kras (CVIM C-terminal sequence). The cDNA for oncogenic val12 variant of human c-Ki-ras-2 4B was obtained from the plasmid pSW11-1 (ATCC). This was then subcloned into the polylinker of a suitable expression vector e.g. pIC147. The Kras was obtained after expression in the E. coli strain, BL21. The expression and purification of c-Ki-ras-2 4B and the val12 variant in E. coli has also been reported by Lowe et al (Lowe P N et al. J. Biol. Chem. (1991) 266 1672-1678).

Incubations with enzyme contained 300nM tritiated farnesyl pyrophosphate (DuPont/New England Nuclear), 120nM ras-CVIM, 50mM Tris HCl pH 8.0, 5mM  $\text{MgCl}_2$ , 10 $\mu\text{M}$   $\text{ZnCl}_2$ , 5mM dithiothreitol and compounds were added at appropriate concentrations in DMSO (3% final concentration in test and vehicle control). Incubations were for 20 minutes at 37 ° and were stopped with acid ethanol as described by Pompliano et al. (Pompliano D L et al (1992) 31 3800-3807). Precipitated protein was then collected onto glass fibre filter mats (B) using a Tomtec<sup>®</sup> cell harvester and tritiated label was measured in a Wallac<sup>®</sup> 1204 Betaplate scintillation counter.

Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general compounds of the Formula I possess an

**SUBSTITUTE SHEET (RULE 26)**

- 29 -

IC<sub>50</sub> in the above test in the range. for example. 0.01 to 200µM. Thus by way of example, the compound

5 {[(2S,4S)-4-acetylsulfanyl-1-(4-nitro-benzyloxycarbonyl)-pyrrolidine-2-carbonyl]-amino}-3(N-methyl-methoxycarbamoyl)-benzoic acid allyl ester (see Example 7) has an IC<sub>50</sub> of approximately 0.5µM. No physiologically unacceptable toxicity was observed at the effective dose for compounds tested of the present invention.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:-

10 (i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration:

(ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon:

(iii) column chromatography (by the flash procedure) and medium pressure  
15 liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

20 (v) the end-products of the Formula I have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and mass spectral techniques: chemical shift values were measured on the delta scale; the following abbreviations have been used: s, singlet; d, doublet; t or tr, triplet; m, multiplet; br, broad:

(vi) intermediates were not generally fully characterised and purity was assessed by  
25 thin layer chromatographic, infra-red (IR) or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus: melting points for the end-products of the Formula I were determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture:

30 and

- 30 -

(viii) the following abbreviations have been used:-

	BOC	<u>tert</u> -butoxycarbonyl
	DCCI	1,3-dicyclohexylcarbodiimide
	DMA	<u>N,N</u> -dimethylacetamide
5	DMAP	4-dimethyl-aminopyridine
	DMF	<u>N,N</u> -dimethylformamide
	DMSO	dimethylsulfoxide
	EDC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide
	EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
10	HOBt	1-hydroxybenzotriazole
	NMM	<u>N</u> -methylmorpholine
	NMM-O	4-methylmorpholine- <u>N</u> -oxide
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
15	TMSI	trimethylsilyliodide
	TPAP	tetrapropylammonium perruthenate

Note in the Schemes only those hydrogen atoms thought to assist clarity have been illustrated (ie not all hydrogen atoms have been illustrated).

20

Example 1 (see Scheme 1)

**(2S,4S)-4-acetylsulfanyl-2[3-nitro-5-(N-methoxy-N-methyl-carbamoyl)-phenylcarbamoyl]-pyrrolidine-1-carboxylic acid 4-nitro-benzyl ester**

25

A mixture of 4-acetylsulfanyl-pyrrolidine-1,2-dicarboxylic acid 1-(4-nitrobenzyl) ester (1(c)) (0.2 g) and 3-amino-N-methoxy-N-methyl-5-nitro-benzamide (1(b)) (0.122 g) and EEDQ (0.201 g) in dichloromethane (20 ml) was stirred at ambient temperature for 16 hours. The solution was then stirred with 0.3M hydrochloric acid (20 ml) for ten minutes. The organic phase was separated, dried over magnesium sulphate and  
30 evaporated under reduced pressure to give a gum. This was purified by chromatography



- 31 -

using 1.ethyl acetate/hexane (50:50) 2.ethyl acetate/hexane (75:25) to give the desired product (1) as a colourless gum (0.132 g).

NMR Spectrum (CDCl<sub>3</sub>)  $\delta$  2.35 (s, 3H), 2.62 (m, 2H), 3.4 (s, 3H), 3.44 (m, 1H), 3.6 (s, 3H), 4.1 (m, 2H), 4.59 (t, 1H), 5.3 (m, 2H), 7.55 (d, 2H), 8.09 (m, 1H), 8.25 (d, 2H), 8.3 (m, 1H), 8.6 (m, 1H), 9.55 (br. s, 1H).

Starting material (1(c)) was synthesised as described in Reference Example 1-4 in European patent no 126587 (Sumitomo).

Starting material (1(b)) was prepared as follows. A mixture of 3-amino-5-nitrobenzoic acid (10 g), pentafluoro-phenol (10 g) and DCCI (11.3 g) was stirred at ambient temperature for 24 hours. The reaction mixture was filtered and the filtrate poured onto a chromatography column which was then eluted with ethyl acetate/hexane (10:90) to give 3-amino-5-nitrobenzoic acid 2,3,4,5,6-pentafluorophenyl ester (1(a)) as a yellow solid (5.8 g).

NMR Spectrum (CDCl<sub>3</sub>)  $\delta$  4.3 (br. s, 2H), 7.7 (tr, 1H), 7.8 (tr, 1H), 8.36 (tr, 1H).

A mixture of (1(a)) (1.0 g), N,O-dimethylhydroxylamine HCl salt (0.84 g) and triethylamine (1.82 ml) in dichloromethane (50 ml) was stirred at ambient temperature for 48 hours. Water (50 ml) was added and the mixture stirred for a further 5 minutes. The organic phase was separated, dried over magnesium sulphate and evaporated under reduced pressure to give a gum. This was purified by chromatography using 1. ethyl acetate/hexane (10:90), 2. ethyl acetate/hexane (50:50) as eluents to give starting material 3-amino-N-methoxy-N-methyl-5-nitro benzamide (1(b)) as a yellow solid (0.55 g).  
NMR Spectrum: (CDCl<sub>3</sub>)  $\delta$  3.36 (s, 3H), 3.58 (s, 3H), 7.26 (tr, 1H), 7.56 (tr, 1H), 7.90 (tr, 1H).

Example 2 (see Scheme 2)

**(2*S*,4*S*)-4-acetylsulfanyl-2[3-(N-methoxy-N-methylcarbamoyl)-5-nitro-phenylcarbamoyl]-pyrrolidine-1-carboxylic acid allyl ester**

A mixture of (2*S*,4*S*)-4-acetylsulfanyl-pyrrolidine-1,2-dicarboxylic acid 1-allyl ester (1(d)) (0.2 g), 1(b) (0.165 g), and EEDQ (0.271 g), in dichloromethane (20 ml) was stirred at ambient temperature for 16 hours. The solution was then stirred with 0.3M

**SUBSTITUTE SHEET (RULE 26)**

- 32 -

hydrochloric acid for a further 10 minutes. The organic phase was then separated, dried over magnesium sulphate and evaporated under reduced pressure. The product obtained was purified by column chromatography using ethyl acetate/hexane (50:50) as eluent to give the desired product (2) as a colourless gum (0.152 g).

5 NMR Spectrum (CDCl<sub>3</sub>)  $\delta$  2.33 (s, 3H), 2.62 (m, 2H), 3.38 (m, 1H), 3.4 (s, 3H), 3.6 (s, 3H), 4.05 (m, 2H), 4.59 (tr, 1H), 4.69 (d, 2H), 5.3 (m, 2H), 5.95 (m, 1H), 8.14 (t, 1H), 8.28 (tr, 1H), 8.6 (tr, 1H), 9.7 (br.s, 1H).

Synthesis of starting material (1(d)) is described as "Compound (A)" on page  
10 31 of International Patent Application No. WO 92/17479 (Imperial Chemical Industries).  
Synthesis of starting material (1(b)) is described in Example 1.

Example 3 (see Scheme 3)

**5-{{{(2S,4S),4-acetylsulfanyl-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine-2-carbonyl}-**  
15 **amino}-isophthalic acid 1-allyl ester 3-methyl ester**

DMF (0.07 ml) was added to a stirred solution of oxalyl chloride (0.078 ml) in dichloromethane (20 ml) cooled to -20° under an argon atmosphere. After 15 minutes a solution of (1(c)) (0.3 g; see Example 1) in dichloromethane was added followed by a  
20 solution of N-methylmorpholine (0.099 ml) in dichloromethane (2 ml). After a further 15 minutes a solution of 5-amino-isophthalic acid allyl ester methyl ester (3(b)) (0.192g) in dichloromethane (5 ml) was added again followed by a solution of N-methylmorpholine (0.099 ml) in dichloromethane (2 ml). The mixture was allowed to warm to ambient temperature and stirred for 16 hours. The reaction mixture was poured onto a flash column  
25 and eluted with 1. ethyl acetate/hexane (50:50) and, 2. ethyl acetate/hexane (75:25) to give the desired end product (3) as a colourless gum (0.24 g).

NMR Spectrum (CDCl<sub>3</sub>)  $\delta$  2.33 (s, 3H), 2.62 (m, 2H), 3.45 (m, 1H), 3.95 (s, 3H), 4.03 (m, 1H), 4.17 (m, 1H), 4.57 (tr, 1H), 4.85 (m, 2H), 5.32 (m, 2H), 5.36 (m, 2H), 6.05 (m, 1H), 7.51 (m, 2H), 8.20 (m, 2H), 8.32  
30 (m, 2H), 8.34 (s, 1H), 9.2 (br. s, 1H).

- 33 -

Starting material (3(b)) was synthesised as follows. A mixture of mono-methyl-5-nitroisophthalate (13.8 g), allyl bromide (7.96 g), potassium carbonate (13.94 g) and DMF (160ml) was stirred at ambient temperature for 4.5 h. The solid was filtered and DMF was evaporated away from the filtrate under reduced pressure. The residue was dissolved in diethyl ether (300 ml) and water (100 ml) and stirred for five minutes. The organic layer was separated and washed with saturated sodium bicarbonate solution (220 ml), brine (200ml), dried over magnesium sulphate and evaporated under reduced pressure to give 5-nitro-isophthalic acid allyl ester methyl ester (3(a)) as a yellow oil (14.74 g).

10 NMR spectrum (CDCl<sub>3</sub>)  $\delta$  4.0 (s, 3H), 4.9 (m, 2H), 5.4 (m, 2H), 6.1 (m, 1H), 9.0 (m, 3H).

A mixture of (3(a)) (15.46 g), tin (II) chloride dihydrate (65.78 g) and methanol (200 ml) was stirred at reflux for 4 hours. Methanol was evaporated under reduced pressure and the residue redissolved in ethyl acetate (400 ml). Ammonia solution (sp. g. 0.880) was added dropwise until the mixture reached pH 8 and no more precipitate was being formed. The solid was then filtered and the filtrate was washed with water (100 ml), brine (100 ml), dried over magnesium sulphate and evaporated under reduced pressure to give starting material 3(b) as a yellow solid (13.56 g).

NMR spectrum (CDCl<sub>3</sub>)  $\delta$  3.91 (s, 3H), 3.94 (s, 2H), 4.82 (m, 2H), 5.35 (m, 2H), 6.05 (m, 1H), 7.52 (m, 2H), 8.08 (m, 1H).

20

Example 4 (see Scheme 4)

**5-[(2S,4S),4-acetylsulfanyl-1-(carbamoylmethyl)-pyrrolidine-2-carbonyl]-amino-isophthalic acid 1-allyl ester 3-methyl ester**

25

A mixture of 5-[(2S,4S),4-acetylsulfanyl-pyrrolidine-2-carbonyl]-amino-isophthalic acid 1-allyl ester 3-methyl ester TFA salt (4(e)) (0.12 g), iodoacetamide (0.085 g), sodium bicarbonate (0.058 g) and DMF (3.0 ml) was stirred at ambient temperature for 16 h. The DMF was evaporated under reduced pressure and the residue purified by chromatography using 1. ethyl acetate/hexane (60:40), 2. ethyl acetate and, 3.

30

- 34 -

methanol/ethyl acetate (5:95) as eluents to give the desired product 4 as a yellow solid (0.055 g).

NMR spectrum  $\delta$  2.19 (2 tr. 1H), 2.29 (s, 3H), 2.82 (m, 1H), 3.22 (m, 2H), 3.48 (q, 2H), 3.6 (m, 1H), 3.94 (s, 3H), 4.05 (m, 1H), 4.85 (m, 2H), 5.35 (m, 2H), 6.04 (m, 1H), 6.1 (br. s, 1H), 6.30 (br. s, 1H), 8.43 (m, 1H), 8.55 (m, 1H), 10.46 (br. s, 1H).

Starting material 4(e) was prepared as follows. A mixture of (2S,4S)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (1.0 g), EEDQ (1.6 g), Compound (3(b)) (see Example 3) and dichloromethane (100 ml) was stirred at ambient temperature for 16 hours.

The mixture was poured onto a flash column and eluted with 1. ethyl acetate/hexane (80:20) and, 2. ethyl acetate to give

5-{{(2S,4S)-4-hydroxy-1-(tert-butoxycarbonyl)-pyrrolidine-2-carbonyl}-amino}-isophthalic acid 1-allyl ester 3-methyl ester (4(a)) as a colourless gum (0.85 g.).

NMR Spectrum (DMSO-d<sub>6</sub>)  $\delta$  1.34 (2s, 9H), 1.97 (m, 1H), 2.15 (m, 1H), 3.30 (m, 1H), 3.46 (m, 1H), 3.9 (s, 3H), 4.32 (m, 2H), 4.84 (d, 2H), 5.06 (d, 1H), 5.35 (m, 2H), 6.07 (m, 1H), 8.18 (m, 1H), 8.54 (m, 2H).

A mixture of (4(a)) (0.8 g), methanesulphonyl chloride (0.152 ml), triethylamine (0.256 ml), and dichloromethane (20 ml) was stirred at 5° under an argon atmosphere for 10 minutes and then at ambient temperature for 2h. Water (20 ml) was then added and the mixture stirred for another 5 minutes. The organic phase was separated, dried over magnesium sulphate and evaporated under reduced pressure. The product was purified by chromatography using 1. ethyl acetate/hexane (30:70) and, 2. ethyl acetate/hexane (80:20) as eluents to give

5-{{(2S,4S)-4-methanesulfanyloxy-1-(tert-butoxycarbonyl)-pyrrolidine-2-carbonyl}-amino}-isophthalic acid 1-allyl ester 3-methyl ester (4(b)) as a clear oil (0.8 g).

NMR spectrum (CDCl<sub>3</sub>)  $\delta$  1.5 (s, 9H), 2.4 (m, 1H), 2.92 (m, 1H), 3.07 (s, 3H), 3.63 (m, 1H), 3.9 (m, 1H), 3.95 (s, 3H), 4.66 (m, 1H), 4.85 (m, 2H), 5.27 (m, 1H), 5.36 (m, 2H), 6.05 (m, 1H), 8.37 (m, 3H), 9.64 (br. s, 1H).

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- 35 -

A mixture of 4(b) (0.74 g), potassium thioacetate (0.32 g) and acetone (25 ml) was maintained at reflux for 18 hours. The mixture was then cooled to room temperature and acetone evaporated under reduced pressure. The residue was dissolved in a mixture of ethyl acetate (50 ml), 1.5M hydrochloric acid (25 ml), and ice (25 ml). The organic phase  
5 was separated, dried over magnesium sulphate and evaporated under reduced pressure to give a red gum. This was purified by chromatography using 1. ethyl acetate/hexane (30:70) and, 2. ethyl acetate/hexane(70:30) to give  
5-{[(2S,4S),4-acetylsulfanyl-1-(tert-butoxycarbonyl)-pyrrolidine-2-carbonyl]-amino}-isophthalic acid 1-allyl ester 3-methyl ester  
10 (4(c)) as an orange gum (0.48 g).

NMR spectrum (CDCl<sub>3</sub>)  $\delta$  1.5 (s, 9H), 2.32 (s, 3H), 2.56 (m, 2H), 3.33 (m, 1H), 3.93 (s, 3H), 4.04 (m, 2H), 4.52 (tr, 1H), 4.85 (m, 2H), 5.35 (m, 2H), 6.05 (m, 1H), 8.38 (m, 3H), 9.63 (br. s, 1H).

A mixture of (4(c)) (3.6 g) and TFA (80 ml) was stirred at ambient  
15 temperature for 10 minutes. TFA was evaporated under reduced pressure and the residue dissolved in ethyl acetate (200 ml.) and saturated sodium bicarbonate solution (100 ml). This was then stirred for 10 minutes, the organic phase separated, washed with water (100 ml) and brine (100 ml) and dried over magnesium sulphate. The ethyl acetate was removed under reduced pressure and the residue purified by chromatography using 1. ethyl  
20 acetate/hexane (30:70), 2. ethyl acetate/hexane (80:20) as eluents to give 4(f) (the free base which is used in Example 6) as a brown oil (2.3 g). NMR Spectrum (CDCl<sub>3</sub>)  $\delta$  2.05 (m, 1H), 2.30 (s, 3H), 2.42 (br. s, 1H), 2.78 (m, 2H), 3.58 (m, 1H), 3.85 (m, 1H), 3.94 (s, 3H), 3.99 (m, 1H), 4.84 (m, 2H), 5.35 (m, 2H), 6.05 (m, 1H), 8.47 (m, 3H), 9.83 (br. s, 1H).

A mixture of (4(c)) (0.45 g) and TFA (10 ml) was stirred at ambient  
25 temperature for 10 minutes. The TFA was evaporated away under reduced pressure and the residue purified by column chromatography using 1 ethyl acetate/hexane (30:70), 2 ethyl acetate/hexane (60:40), 3 ethyl acetate and, 4 methanol/ethyl acetate (10:90) as eluents to give the desired starting material (4(e)) as a brown gum (0.46 g).  
NMR Spectrum (CDCl<sub>3</sub>)  $\delta$  2.15 (m, 1H), 2.33 (s, 3H), 2.97 (m, 1H), 3.44  
30 (m, 1H), 3.91 (s, 3H), 3.97 (m, 1H), 4.08 (m, 1H), 4.82 (d, 2H), 4.98 (tr, 1H), 5.35 (m, 2H), 6.03 (m, 1H), 8.12 (m, 2H), 8.26 (m, 1H).

SUBSTITUTE SHEET (RULE 26)

- 36 -

Example 5 (see Scheme 5)**5-[[(2S,4S)]-4-acetylsulfanyl-1-acetyl-pyrrolidine-2-carbonyl]-amino}-isophthalic acid 1-allyl ester 3-methyl ester**

A mixture of (4(e)) (0.08 g; see Example 4), triethylamine (0.083 ml), acetic anhydride (0.056 ml) and dichloromethane (5 ml) was maintained at reflux for 16 hours. The mixture was cooled, evaporated under reduced pressure and purified by chromatography using 1 ethyl acetate/hexane (70:30), 2 ethyl acetate and 3 methanol/dichloromethane (5:95) to give the desired product 5 as a colourless gum (0.048 g).

NMR Spectrum (CDCl<sub>3</sub>) δ 2.18 (s, 3H), 2.35 (s, 3H), 2.48 (m, 1H), 2.77 (m, 1H), 3.42 (m, 1H), 3.95 (s, 3H), 4.1 (m, 2H), 4.85 (m, 3H), 5.35 (m, 2H), 6.06 (m, 1H), 8.40 (m, 3H), 9.88 (br. s, 1H).

Starting material 4(e) was prepared as described in Example 4.

Example 6 (see Scheme 6)**5-[[(2S,4S)]-4-acetylsulfanyl-1-phenyloxycarbonyl-pyrrolidine-2-carbonyl]-amino}-isophthalic acid 1-allyl ester 3-methyl ester**

A mixture of (4(f)) (0.07g), phenyl chloroformate (0.026 ml), triethylamine (0.07 ml) and dichloromethane (3 ml) was stirred at ambient temperature for 16 hours. The mixture was then evaporated under reduced pressure to give a gum which was purified by chromatography using 1 dichloromethane, 2 ethyl acetate/hexane (30:70) and 3 ethyl acetate/hexane (60:40) to give the desired product as a colourless gum (0.048 g.).

NMR Spectrum (DMSOd<sub>6</sub>) δ 1.93-2.24 (m, 1H), 2.38 (s, H), 2.70 (m, 1H), 3.63 (m, 1H), 3.91 (d, 3H), 4.18 (m, 2H), 4.60 (m, 1H), 4.87 (tr, 2H), 5.38 (m, 1H), 6.08 (m, 1H), 6.70-7.69 (m, 5H), 8.20-8.53 (m, 3H), 10.61 (d, 1H).

Starting material (4(f)) was prepared as described in Example 4.

Example 7 (see Scheme 7)

**5{[(2S,4S),4-acetylsulfanyl-1-(4-nitro-benzoyloxycarbonyl)-pyrrolidine-2-carbonyl]-amino}-3(N-methyl-methoxycarbamoyl)-benzoic acid allyl ester**

5 A mixture of (1(c)) (0.02 g; see Example 1), 3-amino- 5(N-methyl-methoxycarbamoyl)-benzoic acid allyl ester (7(d)) (0.16 g.), EEDQ (0.25 g) and dichloromethane (20 ml) was stirred for 16 h at ambient temperature. The mixture was then washed with 0.3M hydrochloric acid (30 ml), the organic phase separated, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was  
10 purified by column chromatography using ethyl acetate/hexane (75:25) as eluent to give the desired product 7 as a yellow solid (0.053 g).

NMR Spectrum ( $\text{CDCl}_3$ )  $\delta$  2.33 (s, 3H), 2.60 (m, 2H), 3.38 (s, 3H), 3.42 (m, 1H), 3.60 (s, 3H), 4.04 (m, 1H), 4.15 (m, 1H), 4.55 (m, 1H), 4.83 (m, 2H), 5.30 (m, 2H), 5.35 (m, 2H), 6.04 (m, 1H), 7.52 (m, 2H), 8.10  
15 (m, 3H), 8.18 (m, 2H), 9.12 (br. s, 1H).

Starting material (1(c)) was prepared as described in Example 1. Starting material 7(d) was prepared as follows. A mixture of potassium carbonate (17.00 g), 5-nitroisophthalic acid (52.00 g), allyl bromide and dimethylacetamide (400 ml) was stirred at 90° for 4 h. Dimethylacetamide was evaporated away under reduced pressure  
20 and the residue was dissolved in ethyl acetate, washed with water (2 x 300 ml) and then extracted with aqueous saturated sodium bicarbonate solution (3 x 300 ml). The extracts were combined, acidified to pH 4 with concentrated hydrochloric acid and reextracted with ethyl acetate (2 x 300 ml). The extracts were combined, washed with water (300 ml), dried over magnesium sulphate and evaporated under reduced pressure to give  
25 5-nitro-isophthalic acid 3-allyl ester (7(a)) as a cream solid (39.48 g).

NMR Spectrum ( $\text{CDCl}_3/\text{DMSO-d}_6$ )  $\delta$  4.90 (m, 2H), 5.42 (m, 2H), 6.08 (m, 1H), 9.00 (m, 3H).

A solution of 7(a) (10.00 g), N-hydroxysuccinimide (5.04 g) and DCCl (9.03 g) in dichloromethane (400 ml) was stirred at ambient temperature for 3.5 h. The white  
30 precipitate which formed was filtered off and the filtrate evaporated under reduced pressure

- 38 -

to give a yellow oil. This was purified by flash chromatography eluting with ethyl acetate/hexane (75:25) to give

5-nitro-isophthalic acid 1-(2,5-dioxo-pyrrolidin-1-yl) ester 3-allyl ester (7(b)) as a yellow solid (7.58 g).

5 NMR Spectrum (CDCl<sub>3</sub>)  $\delta$  2.95 (s, 4H), 4.92 (m, 2H), 5.43 (m, 2H), 6.07 (m, 1H), 9.12 (m, 3H).

A mixture of (7(b)) (2.00 g), N,O-dimethylhydroxylamine hydrochloride (0.62 g), triethylamine (0.86 ml) and dichloromethane (60 ml) was stirred at 5° for 30 min and then allowed to warm to ambient temperature and stirred for a further 16 h. The mixture  
10 was poured onto a flash column and eluted with ethyl acetate/hexane (40:60) to give 3-(N-methyl-methoxycarbamoyl)-5-nitro benzoic acid allyl ester (7(c)) as a yellow oil.  
NMR Spectrum (CDCl<sub>3</sub>)  $\delta$  3.43 (s, 3H), 3.58 (s, 3H), 4.90 (m, 2H), 5.40 (m, 2H), 6.07 (m, 1H), 8.71 (m, 1H), 8.76 (m, 1H), 8.95 (m, 1H).

A mixture of (7(c)) (1.11 g), tin(II) chloride dihydrate (4.26 g) and methanol  
15 (60 ml) was heated under reflux for 1 hour. The reaction mixture was cooled and the methanol evaporated away under reduced pressure. The residue was redissolved in ethyl acetate (100 ml) and ammonia solution (sp. g. 0.880) was added dropwise until the solution reached pH 8. The precipitate that formed was filtered and washed with ethyl acetate (2 x 100 ml). The combined filtrate and washings were evaporated under reduced pressure to  
20 give the desired starting material 3-amino-5-(N-methyl-methoxycarbamoyl)-benzoic acid allyl ester (7(d)) as a white solid (0.610 g).

NMR Spectrum (CDCl<sub>3</sub>)  $\delta$  3.35 (s, 3H), 3.59 (s, 3H), 3.90 (br. s, 2H), 4.82 (m, 2H), 5.35 (m, 2H), 6.04 (m, 1H), 7.15 (m, 1H), 7.45 (m, 1), 7.72 (m, 1H).

25

Example 8 (see Scheme 8)

5{[(2S,4S),4-acetylsulfanyl-1-(4-nitro-benzyloxycarbonyl)-pyrrolidine-2-carbonyl]-amino}-3(N-methyl-allyloxycarbamoyl)-benzoic acid allyl ester

30 A mixture of (1(c)) (0.293 g; see Example 1), 3-amino- 5(N-methyl-allyloxycarbamoyl)-benzoic acid allyl ester (8(c)) (0.210 g), EEDQ (0.268 g) and

SUBSTITUTE SHEET (RULE 26)



- 39 -

dichloromethane (20 ml) was stirred at ambient temperature for 16 hours. The mixture was then washed with 0.3M hydrochloric acid (30 ml), dried over magnesium sulphate and placed straight onto a flash column eluting with ethyl acetate/hexane (75:25). The product obtained was placed onto a flash column eluting with methanol/dichloromethane (2.5:97.5) to give the desired product 8 as a clear gum (0.153 g).

NMR Spectrum ( $\text{CDCl}_3$ )  $\delta$  2.33 (s, 3H), 2.61 (m, 2H), 3.40 (s, 3H), 3.42 (m, 1H), 4.04 (m, 1H), 4.15 (m, 1H), 4.26 (d, 2H), 4.55 (m, 1H), 4.83 (m, 2H), 5.30 (m, 6H), 5.75 (m, 1H), 6.04 (m, 1H), 7.53 (m, 2H), 8.12 (m, 2H), 8.21 (m, 3H), 9.12 (br. s, 1H).

10

Starting material (8(c)) was prepared as follows. A mixture of 7(b) (2.00 g; see Example 7), N-methylhydroxylamine hydrochloride (1.06 g) triethylamine (1.72 ml) and dichloromethane (60 ml.) was stirred at 50° for 30 minutes. It was then allowed to warm to ambient temperature and stirred for a further 16 hours. The reaction mixture was then poured directly onto a flash column eluting with ethyl acetate/hexane (50:50) to give 3-(N-methyl-hydroxycarbamoyl)-5-nitro-benzoic acid allyl ester (8(a)) as a cream solid (1.43 g).

15

NMR Spectrum ( $\text{CDCl}_3$ )  $\delta$  3.48 (s, 3H), 4.90 (m, 2H), 5.42 (m, 2H), 6.05 (m, 1H), 8.28 (br. s, 1H), 8.55 (m, 1H), 8.63 (m, 1H), 8.96 (m, 1H).

20

A mixture of (8(a)) (0.60 g), allyl bromide (0.28 g), potassium carbonate (0.59 g) and DMF (20 ml) was stirred for 3 hours at ambient temperature under an argon atmosphere. The dimethyl formamide was then evaporated under reduced pressure and the residue dissolved in ethyl acetate (50 ml) and water (50ml). The organic phase was separated, washed with brine (50 ml), dried over magnesium sulphate and evaporated under reduced pressure to dryness to give 3-(N-methyl-allyloxycarbamoyl)-5-nitro-benzoic acid allyl ester (8(b)) as a yellow oil (0.571 g).

25

NMR Spectrum  $\delta$  3.47 (s, 3H), 4.25 (m, 2H), 4.90 (m, 2H), 5.35 (m, 4H), 5.65 (m, 1H), 6.06 (m, 1H), 8.73 (m, 1H), 8.78 (m, 1H), 8.95 (m, 1H).

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- 40 -

A mixture of (8(b)) (0.523 g), tin(II) chloride dihydrate (1.84 g) and ethyl acetate (50 ml) was heated under reflux for 6 hours. The mixture was allowed to cool to ambient temperature and ammonia solution (sp. g. 0.880) was added dropwise until the solution reached pH 8. The white precipitate which had formed was filtered off, washed with ethyl acetate (2 x 50 ml) and the combined washings and filtrate evaporated to dryness to give the desired starting-material (8(c)) as a yellow oil (0.472 g).

NMR Spectrum (CDCl<sub>3</sub>)  $\delta$  3.38 (s, 3H), 3.88 (m, 2H), 4.25 (d, 2H), 4.80 (m, 2H), 5.32 (m, 4H), 5.75 (m, 1H), 6.03 (m, 1H), 7.15 (m, 1H), 7.45 (m, 1H), 7.75 (m, 1H).

Example 9 (see Scheme 9)

**5-[[[(2S,4S),1-(allyloxycarbonyl)-4-sulfanyl-pyrrolidine-2-carbonyl]-amino]-3-(N-methyl-allyloxycarbonyl)-benzoic acid allyl ester**

An aqueous solution of 0.1M sodium hydroxide (4.41 ml) was added to a solution of 5-[[[(2S,4S),4-acetylsulfanyl-1-(allyloxycarbonyl)-pyrrolidine-2-carbonyl]-amino]-3-(N-methyl-allyloxycarbonyl)-benzoic acid allyl ester (9(a)) in allyl alcohol (15 ml) and the mixture was then stirred at ambient temperature for 1 hour. Hydrochloric acid (1.5M) was then added to bring the solution to pH3 and it was then evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (40 ml) and washed with water (2 x 40 ml). The organic phase was separated, dried over magnesium sulphate and evaporated to dryness to give a yellow foam. This was purified by chromatography using ethyl acetate/hexane (75:25) as eluent to give the desired product 9 as a yellow gum (0.148 g).

NMR Spectrum (CDCl<sub>3</sub>)  $\delta$  1.88 (d, 2H), 2.62 (m, 2H), 3.37 (s, 3H), 3.45 (m, 2H), 3.60 (s, 3H), 4.08 (m, 1H), 4.52 (tr, 1H), 4.65 (m, 2H), 4.83 (m, 2H), 5.35 (m, 4H), 6.00 (m, 2H), 8.10 (m, 1H), 8.15 (m, 1H), 8.21 (m, 1H), 9.15 (br. s, 1H).

Starting material 9(a) was prepared as follows. A mixture of 7(d) (0.568 g; see Example 7), 1(d) (0.645 g; see Example 20), EEDQ (0.585 g) and dichloromethane (50

**SUBSTITUTE SHEET (RULE 26)**

- 41 -

ml) was stirred at ambient temperature for 16 hours. The mixture was then washed with 0.3M hydrochloric acid(50 ml), dried over magnesium sulphate and applied to a flash column eluting with ethyl acetate/hexane (75:25). It was further purified with a second column eluting with ethyl acetate/hexane (50:50) to give the desired starting material (9(a))

5 as a colourless gum (0.401 g).

NMR Spectrum (CDCl<sub>3</sub>) δ 2.33 (s, 3H), 2.60 (m, 2H), 3.37 (s, 3H), 3.40 (m, 1H), 3.61 (s, 3H), 4.02 (m, 1H), 4.13 (m, 1H), 4.58 (tr, 1H), 4.68 (m, 2H), 4.83 (m, 2H), 5.35 (m, 4H), 6.00 (m, 2H), 8.10 (m, 1H), 8.14 (m, 1H), 8.22 (m, 1H), 9.30 (br. s, 1H).

10

Example 10 (see Scheme 10)

**5-[((2S,4S))-1-allyloxycarbonyl-4-sulfanyl-pyrrolidin-2-yl-methyl]-carbamoyl]-pyridine-2-carboxylic acid methyl ester**

15

To a stirring solution of

5-[((2S,4S))-1-allyloxycarbonyl-4-BOCsulfanyl-pyrrolidin-2-yl-methyl]-carbamoyl]-pyridine-2-carboxylic acid methyl ester (10(a)) (991 mg; 2.07 mmole) in dichloromethane, TFA (6 mL; 78 mmole) was added dropwise. The solution was stirred, under argon, for 4 hours. The solvent and excess TFA were removed in vacuo. The residue was azeotroped with toluene (2 x 10 mL). Keeping exposure to air to a minimum the resultant oil was triturated with diethyl ether (20 mL). The resultant solid was washed with cold diethyl ether (10 mL) and dried under high vacuum yielding the desired product 10 as a cream solid, 654 mg (76%).

20

[4] has NMR (CDCl<sub>3</sub>; 250 MHz) δ 1.70 (m, 1H), 1.75 (d, 1H), 2.63-2.77 (m, 1H), 3.15-3.50 (m, 3H), 3.90-4.00 (m, 1H), 4.05 (s, 3H), 4.07-4.23 (m, 2H), 4.63 (m, 2H), 5.23-5.37 (m, 2H), 5.85-6.03 (m, 1H), 8.22 (d, 1H), 8.35 (dd, 1H), 8.95 (s(br), 1H), 9.20 (s, 1H).

25

MS (FAB) m/z 380 (M+H)<sup>+</sup>

Anal. C<sub>17</sub>H<sub>21</sub>N<sub>3</sub>O<sub>5</sub>S. 0.33 C<sub>2</sub>HF<sub>3</sub>O<sub>2</sub> 417: C 50.9 (50.8), H 5.3 (5.1), N 10.1 (10.1).

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- 42 -

Starting material (10(c)) was prepared as follows. Pyridine 2,5-dicarboxylic acid 2-methyl ester (10(a)) (9.0 g; 0.05 mole) was added to stirring thionyl chloride (25 mL) and the mixture refluxed gently for 2.5 hours. The excess thionyl chloride was removed in vacuo and the residual solid azeotroped with toluene (2 x 25 mL) to give

5 5-chlorocarbonyl-pyridine-2-carboxylic acid methyl ester (10(b)) which was used crude in the next reaction.

To a stirring solution of compound (15(b)) (Example 15) (220 mg; 0.7 mmole) in acetonitrile (6 mL) was added a solution of (10(b)) (0.7 mmole) in acetonitrile (4 mL). Triethylamine (0.29 mL; 2.1 mmole) was added and the solution stirred for 23 hours. The

10 solvent and excess triethylamine were removed in vacuo and the residue partitioned between chloroform and water. The organic phase was washed with water, aqueous sodium hydrogen carbonate solution and brine, dried over magnesium sulphate and taken to dryness. The residual orange gum was flash chromatographed on kieselgel 9385, eluting initially with iso-hexane then with increasing proportions of ethyl acetate. The desired

15 starting material 10(c) was isolated as a white foam (200 mg; 60%).

NMR (CDCl<sub>3</sub>; 250 MHz) 1.50 (s, 9H), 1.80 (m, 1H), 2.62-2.75 (m, 1H), 3.30-3.37 (m, 1H), 3.39-3.50 (m, 1H), 3.68-3.80 (m, 1H), 3.83-3.95 (m, 1H), 4.03 (s, 3H), 4.13-4.28 (m, 2H), 4.62 (m, 2H), 5.20-5.37 (m, 2H), 5.87-6.02 (m, 1H), 8.2 (d, 1H), 8.3 (dd, 1H), 8.87 (s, 1H), 9.2 (s, 1H).

20 MS (FAB) m/z 480 (M+H)

Anal. C<sub>22</sub>H<sub>29</sub>N<sub>3</sub>O<sub>7</sub>S 479 :C 55.1 (55.1), H 6.4 (6.1), N 8.5 (8.8).

Example 11 (see Scheme 11)

(2S,4S)-2-[[5-ethoxycarbonyl-thiophene-2-carbonyl]-amino]-methyl}-4-

25 sulfanyl-pyrrolidine-1-carboxylic acid allyl ester

TFA (2mL; 26 mmole) was added to a stirring solution of

(2S,4S)-2-[[5-ethoxycarbonyl-thiophene-2-carbonyl]-amino]-methyl}-4-

BOCsulfanyl-pyrrolidine-1-carboxylic acid allyl ester (11(b)) (130mg ; 0.26 mmole) in

30 dichloromethane (20 mL). The solution was stirred under argon for 19 hours. The solvent

- 43 -

and excess TFA were removed in vacuo and the residue dried under high vacuum to give the desired product 11 as a water-white gum (64%).

NMR (CDCl<sub>3</sub>; 250 MHz) δ 1.38 (t, 3H), 1.55-1.70 (m, 1H), 1.75 (d, 1H), 2.60-2.76 (m, 1H), 3.10-3.50 (m, 3H), 3.80-3.95 (m, 1H), 4.05-4.25 (m, 2H), 4.38 (q, 2H), 4.70 (m, 2H), 5.20-5.40 (m, 2H), 5.85-6.05 (m, 1H), 7.47 (d, 1H), 7.73 (d, 1H), 8.52 (s(br), 1H)  
MS (FAB) m/z 399 (M+H)<sup>+</sup> Anal. C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub> 0.5 C<sub>2</sub>HF<sub>3</sub> O<sub>2</sub> 455:  
C 47.6 (47.5), H 5.2 (4.9), N 6.1 (6.15).

Starting material 11(b) was prepared in an analogous manner to the equivalent step in Example 10 but with addition of 5-chlorocarbonyl-thiophene-2-carboxylic acid-ethyl-ester (11(a)) to compound (15(b)) (Example 15) with similar chromatographic work up. 11(b) is a tacky water white gum. Yield 60%. Preparation of (11(a)) is described in Journal of the American Pharmaceutical Association (Sci. Ed.) Vol. 41 pp 273-276 (1952).

NMR of 11(b): (CDCl<sub>3</sub>; 250 MHz) δ 1.4 (t, 3H), 1.5 (s, 9H), 1.70-1.85 (m, 1H), 2.57-2.73 (m, 1H), 3.26-3.36 (m, 1H), 3.38-3.50 (m, 1H), 3.65-3.87 (m, 2H), 4.10-4.25 (m, 2H), 4.35 (q, 2H), 4.65 (m, 2H), 5.20-5.38 (m, 2H), 5.85-6.04 (m, 1H), 7.47 (d, 1H), 7.72 (d, 1H), 8.45 (s(br), 1H).

MS (FAB) m/z 499 (M+H)<sup>+</sup>, other m/z 183

Anal. C<sub>22</sub>H<sub>30</sub>N<sub>2</sub>O<sub>7</sub>S<sub>2</sub> 498 C 53.4 (53.0), H 6.3 (6.1), N 5.5 (5.6)

Example 12 (see Scheme 12)

**N-(3,4-dichlorobenzyl)-N'-((2S,4S),4-sulfanyl-pyrrolidin-2-yl-methyl) thiophene-2,5-dicarboxamide**

To a stirring solution of N-(3,4-dichlorobenzyl)-N'-((2S,4S),-1-allyloxycarbonyl-4-sulfanyl-pyrrolidin-2-yl-methyl) thiophene-2,5-dicarboxamide (12(e)) (59 mg; 0.1 mmole) in dichloromethane (10 mL), under argon, was added trimethylsilyliodide (0.35 mL; 0.25 mmole). After 20 hours at ambient temperature the dichloromethane and excess trimethylsilyliodide were removed in vacuo and the residue treated with methanol (3 mL). The insoluble material was treated with further methanol (2

- 44 -

x 3 mL) and then triturated with diethyl ether to yield a solid which was filtered and dried to give the desired product 12 as a light brown solid (59%).

NMR (DMSO-d<sub>6</sub>; 250 MHz)  $\delta$  1.65-1.90 (m, 1H), 2.50-2.62 (m, 1H), 3.20-3.40 (m, 2H), 3.55-3.70 (m, 2H), 3.75-3.90 (m, 2H), 4.45 (d, 2H), 7.32 (m, 1H), 7.58 (m, 2H), 7.73 (d, 1H), 7.78 (d, 1H), 8.68 (br, 1H), 8.88 (t, 1H), 9.22 (t, 1H).  
MS (FAB) m/z 444 (M+H)<sup>+</sup> other 111, 312 Anal. C<sub>18</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub> 1.25 HI 0.5 C<sub>4</sub>H<sub>10</sub>O 640 C 37.6 (37.5), H 3.5 (3.9), N 6.5 (6.6).

Starting material (12(e)) was prepared as follows. To a stirring solution of 3,4-dichlorobenzylamine (0.53 mL; 4.0 mmole) in acetonitrile (10 mL) was added triethylamine (1.67 mL; 12.0 mmole) and a solution of (11(a)) (0.87g; 4.0 mmole, see Example 11) in acetonitrile (20 mL). The solution was stirred at ambient temperature, under argon, for 22 hours. The solvent and excess triethylamine were removed in vacuo and the residue partitioned between chloroform and water. The organic phase was washed with water and brine, dried over magnesium sulphate and vacuumed to dryness to give 5-(3,4-dichlorobenzyl-carbamoyl)-thiophene-2-carboxylic acid ethyl ester (12(a)) as a cream solid (90%).

NMR (CDCl<sub>3</sub>; 250 MHz)  $\delta$  1.40 (t, 3H), 4.38 (q, 2H), 4.57 (d, 2H), 6.47 (t(br), 1H), 7.28 (m, 1H), 7.42 (m, 2H), 7.48 (d, 1H), 7.73 (d, 1H) MS (CI) m/z 358 (M+H)<sup>+</sup>  
Anal. C<sub>15</sub>H<sub>13</sub>Cl<sub>2</sub>NO<sub>3</sub>S 358: C 50.4 (50.3), H 3.8 (3.7), N 3.9 (3.9).

Aqueous 1M sodium hydroxide (16.3 mL; 16.3 mmole) was added to a stirring solution of (12(a)) (1.17g; 3.3 mmole) in ethanol (70 mL). The reaction mixture was stirred at ambient temperature for 19 hours, reduced to a small volume, diluted with water and adjusted to pH 2 by addition of 2M hydrochloric acid. The filtered solid was washed with water and dried in vacuo to give 5-(3,4-dichlorobenzyl-carbamoyl)-thiophene-2-carboxylic acid (12(b)) as a white solid (83%).

NMR (DMSO d<sub>6</sub>; 200MHz)  $\delta$  4.43 (d, 2H), 7.3 (dd, 1H), 7.58 (m, 2H), 7.68 (d, 1H), 7.78 (d, 1H), 9.28 (t, 1H) MS (CI) m/z 330 (M+H)<sup>+</sup>  
Anal. C<sub>13</sub>H<sub>9</sub>Cl<sub>2</sub>NO<sub>3</sub>S 330 C 47.3 (47.3), H 2.7 (2.7), N 4.2 (4.2).

SUBSTITUTE SHEET (RULE 26)

- 45 -

A stirring solution of (12(b)) (495mg; 1.5 mmole) in dichloromethane (25 mL) was cooled in an ice bath and DMF (1 drop) and oxalyl chloride (0.175 mL : 2.0 mmole) added dropwise. The solution was stirred at ambient temperature under argon for 4 hours. The dichloromethane and excess oxalyl chloride were removed in vacuo. The residue was  
5 azeotroped with toluene (2 x 15 mL) to give 5-(3,4-dichlorobenzyl-carbamoyl)-thiophene-2-carbonyl-chloride (12(c)) which was used crude in the next step.

Triethylamine (0.83 mL; 4.5 mmole) and a solution of compound (15(b)) (Example 15) (316 mg; 1.0 mmole) in acetonitrile (10 mL) were added to a stirring mixture of (12(c)) (1.5 mmole) in acetonitrile (15 mL) and stirred at ambient temperature under  
10 argon for 19 hours. The acetonitrile and excess triethylamine were removed in vacuo and the residue partitioned between chloroform and water. The organic phase was washed with water and brine, dried over magnesium sulphate and vacuumed to dryness to give N-(3,4-dichlorobenzyl)-N'-((2S,4S),-1-allyloxycarbonyl-4-BOCsulfanyl-pyrrolidin-2-yl-methyl) thiophene-2,5-dicarboxamide (12(d)) as a tacky  
15 brown solid (95%).

NMR (CDCl<sub>3</sub>; 200 MHz)  $\delta$  1.5 (s, 9H), 1.65-1.85 (m, 1H), 2.47-2.73 (m, 1H), 3.25-3.50 (m, 2H), 3.65-3.85 (m, 2H), 4.10-4.23 (m, 2H), 4.57 (d, 2H), 4.64 (m, 2H), 5.20-5.40 (m, 2H), 5.85-6.05 (m, 1H), 6.45 (t, 1H), 7.20 (dd, 1H), 7.40 (m, 2H), 7.46 (d, 1H), 7.53 (d, 1H), 8.47 (br, 1H) MS (FAB)  $m/z$  628 (M+H)<sup>+</sup> Anal. C<sub>27</sub>H<sub>31</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>6</sub>S.H<sub>2</sub>O  
20 646 C 50.2 (50.2), H 4.9 (5.1), N 6.5 (6.5).

TFA (5 mL; 65 mmole) was added to a stirred solution of (12(d)) (600 mg; 0.93 mmole) in dichloromethane (25 mL). The solution was stirred at ambient temperature under argon for 4 hours, solvent and excess TFA were removed in vacuo and the residue  
25 azeotroped with toluene to give the desired starting material (12(e)).

NMR (CDCl<sub>3</sub>; 250 MHz)  $\delta$  1.55-1.75 (m, 1H), 1.75 (d, 1H), 2.50 - 2.72 (m, 1H), 3.12-3.43 (m, 1H), 3.65-3.90 (m, 2H), 4.03-4.20 (m, 2H), 4.54 (d, 2H), 4.63 (m, 2H), 5.17-5.37 (m, 2H), 5.85-6.03 (m, 1H), 6.63 (br, 1H), 7.10-7.55 (m, 5H), 8.5 (br, 2H)  
MS (FAB)  $m/z$  528 (M+H)<sup>+</sup> Anal. C<sub>22</sub>H<sub>23</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub> 0.33 C<sub>4</sub>H<sub>10</sub>O 0.3 C<sub>2</sub>HF<sub>3</sub>O<sub>2</sub>  
30 586.5 C 49.0 (49.0), H 4.5 (4.6), N 7.2 (7.2).

SUBSTITUTE SHEET (RULE 26)

- 46 -

Example 13 (see Scheme 13)

**5-[N-(3,4-dichlorobenzyl)carbamoyl]-N-((2S,4S)-4-sulfanylpyrrolidin-2-yl-methyl)pyridine-2-carboxamide**

5                    5-[N-(3,4-dichlorobenzyl)carbamoyl]-N-((2S,4S)-1-allyloxycarbonyl-4-sulfanylpyrrolidin-2-yl-methyl)pyridine-2-carboxamide (13(e)) was treated with trimethylsilyliodide in similar manner to compound (12(e)) in Example 12. The desired product 13 was obtained as a medium brown solid ( 26% ).

NMR (DMSO-d<sub>6</sub>; 200 MHz)  $\delta$  1.70-1.82 (m, 1H), 3.15-3.40 (m, 2H), 3.55-3.90 (m, ?H),  
10 4.52 (d, 2H), 7.35 (dd, 1H), 7.60 (m, 2H), 8.18 (d, 1H), 8.47 (dd, 1H), 8.75 (br, 1H), 9.10 (d, 1H), 9.28 (t + ?, 2H), 9.42 (t, 1H).

MS (FAB) m/z 439 (M+H)<sup>+</sup>. Anal. C<sub>19</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>2</sub>S. 1.5 H<sub>2</sub>O. 0.33 C<sub>4</sub>H<sub>10</sub>O 655.7  
C 37.4 (37.2), H 3.4 (3.7), N 8.1 (8.5).

15                    Starting material (13(e)) was prepared as follows. 5-chlorocarbonyl-pyridine-2-carboxylic acid methyl ester was reacted with 3,4-dichlorobenzylamine analogously with preparation of compound (12(a)) in Example 12 to obtain 5(3,4-dichlorobenzylcarbamoyl)-pyridine-2-carboxylic acid methyl-ester (13(a)) as a cream solid (61%).

NMR (CDCl<sub>3</sub>; 250 MHz).  $\delta$  4.05 (s, 3H), 4.62 (d, 2H), 6.80 (t(br), 1H), 7.22 (dd, 1H), 7.43  
20 (m, 2H), 8.20 (d, 1H), 8.30 (m, 1H), 9.08 (d, 1H). MS (CI) m/z 339 (M+H)<sup>+</sup>  
Anal. C<sub>15</sub>H<sub>12</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub> 339 C 53.2 (53.1), H 3.5 (3.6), N 8.1 (8.3).

Compound (13(a)) was treated in an analogous manner to compound (12(a)) in Example 12 to obtain 5(3,4-dichlorobenzylcarbamoyl)-pyridine-2-carboxylic acid (13(b))  
25 as an off-white solid (82%).

NMR (DMSO-d<sub>6</sub>; 200MHz)  $\delta$  4.50 (d, 2H), 7.33 (dd, 1H), 7.58 (m, 2H), 8.13 (d, 1H), 8.37 (dd, 1H), 9.12 (d, 1H), 9.40 (t, 1H) MS (CI) m/z 325 (M+H)<sup>+</sup>  
Anal. C<sub>14</sub>H<sub>10</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>. H<sub>2</sub>O 343 C 48.9 (48.9), H 3.5 (3.5), N 8.0 (8.2).

Compound (13(b)) was treated in an analogous manner to compound (12(b))  
30 in Example 12 to give 5(3,4-dichlorobenzylcarbamoyl)-pyridine-2-carbonylchloride (13(c)) which was used crude in the next reaction.

**SUBSTITUTE SHEET (RULE 26)**



- 47 -

Compound (13(c)) was reacted with compound (15(b)) (Example 15) in a similar manner to compound (12(c)) in Example 12 to give 5-[N-(3,4-dichlorobenzyl)carbamoyl]-N-((2S,4S)-1-allyloxycarbonyl-4-BOCsulfanylpyrrolidin-2-yl-methyl)pyridine-2-carboxamide as a light brown solid (13(d)) (81%).

5 NMR (CDCl<sub>3</sub>; 250 MHz)  $\delta$  1.50 (s, 9H), 1.73-1.90 (m, 1H), 2.50-2.65 (m, 1H), 3.20-3.30 (m, 1H), 3.62-3.80 (m, 2H), 4.10-4.27 (m, 2H), 4.65 (d?, 4H), 5.18-5.38 (m, 2H), 5.83-6.05 (m, 1H), 6.80 (t(br), 1H), 7.20-7.28 (m, 2H), 7.40-7.48 (m, 2H), 8.23 (s, 2H), 8.75 (br, 1H), 8.98 (d?, 1H).

MS (FAB) m/z 623 (M+H)<sup>+</sup> Anal. C<sub>28</sub>H<sub>32</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>6</sub>S 623 C 53.8 (53.9), H 5.1 (5.2), N 8.9 (9.0) mp 136-137.5°C.

Compound (13(d)) was treated in a similar manner to compound (12(d)) in Example 12 to give the desired starting material (13(e)) as a light brown solid (64%).

15 NMR (CDCl<sub>3</sub>; 250 MHz)  $\delta$  1.70 (d, 1H), 1.80-2.00 (m, 1H), 2.52-2.65 (m, 1H), 3.05-3.25 (m, 2H), 3.60-3.85 (m, 2H), 4.05-4.20 (m, 2H), 4.60 (d?, 4H), 5.18-5.33 (m, 2H), 5.85-6.03 (m, 1H), 6.80 (br, 1H), 7.20 (dd, 1H), 7.40-7.47 (m, 2H), 8.23 (s, 2H), 8.78 (br, 1H), 9.0 (s, 1H). MS (FAB) m/z 523 (M+H)<sup>+</sup>

Anal. C<sub>23</sub>H<sub>24</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>4</sub>S. 0.1 C<sub>2</sub>HF<sub>3</sub>O<sub>2</sub> 534.4

C 52.4 (52.1), H 4.6 (4.5), n 10.3 (10.5) mp 101 -105°C

20

Example 14 (see Scheme 14)

**1-hydroxy-4-(((2S,4S),4-sulfanyl-pyrrolidin-2-yl-methyl)-amino-sulfonyl)naphthalene-2-carboxylic-acid**

25 To a stirring solution of  
1-hydroxy-4-(((2S,4S),1-allyloxycarbonyl-4-sulfanyl-pyrrolidin-2-yl-methyl)-aminosulfonyl)-naphthalene-2-carboxylic-acid (14(c)) (47.5 mg; 0.1 mmole) in dichloromethane (10 mL) was added TMSI (0.56 mL; 0.4 mmole). The solvent and excess TMSI were removed in vacuo after 6 hours. Methanol (5 mL) was added to the residue  
30 and then removed in vacuo from the solution. The residue was triturated with diethyl ether, filtered and dried in vacuo to obtain the desired product 14 as a brown solid (74%).

SUBSTITUTE SHEET (RULE 26)

- 48 -

NMR (DMSO-d<sub>6</sub>; 250 MHz)  $\delta$  1.45-1.62 (m, 1H), 2.25-2.45 (m, 1H), 2.90-3.25 (m, 3H), 3.45-3.70 (m, 2H), 7.72 (m, 1H), 7.85 (m, 1H), 8.12 (m, 1H), 8.38-8.60 (m, 2H), 9.15 (br, 1H)

MS (FAB) m/z 383 (M+H)<sup>+</sup>

5 Anal. C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub>. 1.25 H<sub>2</sub>O. 0.5 C<sub>4</sub>H<sub>10</sub>O 579 C 37.0 (37.3), H 4.1 (4.2), N 4.8 (4.8).

Starting material (14(c)) was prepared as follows. Compound (15(b)) (Example 15) and 1-hydroxy-4-chlorosulfonyl-naphthalene-2-carboxylic acid (14(a)) were coupled in a similar manner to the equivalent step in Example 15 to give

10 1-hydroxy-4-(((2S,4S),

1-allyloxycarbonyl-4-BOCsulfonyl-pyrrolidin-2-yl-methyl)-aminosulfonyl]-naphthalene-2-carboxylic-acid (14(b)) as a light brown solid (80%).

NMR (CDCl<sub>3</sub>; 250 MHz)  $\delta$  1.45 (s, 9H), 1.50-1.75 (m, 1H), 2.28-2.42 (m, 1H), 2.96-3.10 (m, 2H), 3.48-3.60 (m, 1H), 3.80-3.90 (m, 1H), 3.95-4.05 (m, 1H), 4.47 (m, 2H), 4.53-4.63 (m, 1H), 7.55 (m, 1H), 7.67 (m, 1H), 8.50 (m, 2H), 8.70 (m, 1H) MS (FAB) M+Na<sup>+</sup> 589, 15 other 317, 261 Anal. C<sub>25</sub>H<sub>30</sub>N<sub>2</sub>O<sub>9</sub>S<sub>2</sub>.H<sub>2</sub>O.0.8 C<sub>3</sub>H<sub>15</sub>N 664.8 C 53.7 (53.8), H 6.7 (6.6), N 5.9 (5.9).

2M Aqueous sodium hydroxide (5 mL: 10.0 mmole) was added to a stirring 20 solution of (14(b)) (333mg; 0.5 mmole) in methanol (5 mL). The solution was evaporated to dryness after 42 hours and the residue dissolved in water (10 mL). The solution was adjusted to pH 2 with 2M hydrochloric acid and the solid was filtered, washed with water and dried in vacuo to give the desired starting material (14(c)) as a white solid (72%).

NMR (CDCl<sub>3</sub>; 200 MHz)  $\delta$  1.48-1.70 (m, 2H), 2.38-2.52 (m, 1H), 25 2.85-3.40 (m, 2H), 3.90-4.05 (m, 2H), 4.40-4.60 (m, 3H), 5.10-5.35 (m, 3H), 5.70-5.95 (m, 2H), 6.20-6.45 (br, 1H), 7.57-7.90 (m, 3H), 8.43-8.70 (m, 4H)

MS (FAB) m/z 467 (M+H)<sup>+</sup> Anal. C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>7</sub>S<sub>2</sub>. 0.5 H<sub>2</sub>O 475 C 50.6 (50.5), H 4.8 (4.8), N 6.0 (5.9).

30

Example 15 (see Scheme 15)

**(2S)-2-{3-[(2S,4S)-4-sulfanyl-pyrrolidin-2-yl-methyl]-sulfamoyl}-benzoylamino}-4-methylsulfanyl-butyric acid methyl ester**

5 TFA (2.0 mL) was added to a stirred solution of (2S)-2-{3-[(2S,4S)-4-BOCsulfanyl-pyrrolidin-2-yl-methyl]-sulfamoyl}-benzoylamino}-4-methylsulfanyl-butyric acid methyl ester (15(d)) (101 mg, 0.18 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) at room temperature under argon. After 1 h the reaction mixture was concentrated to a dryness, azeotroped with toluene (3 x 10 mL) and dried to yield the  
10 desired product 15 as a colourless gum: 101.8 mg (99%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 250MHz) δ 1.6-1.8 (1H, m); 2.0 (1H, d, SH); 2.1-2.4 (5H, m); 2.52.65 (3H, m); 3.15-3.4 (3H, m) 3.45-3.65 (1H, m); 3.7-3.85 (4H, m) 3.9-4.1 (1H, m); 4.85-5.0 (1H, m); 7.55-7.7 (2H, m) 7.8 (1H, s); 8.0 (1H, d); 8.1 (1H, d); 8.3 (1H, s); 9.0-9.4 (1H, s); 10.0-10.4 (1H, s).

15 MS (ESP+) m/z 462 (M+H)<sup>+</sup>.

Starting material (15(d)) was prepared as follows. Triethylamine (3.0mL, 21.5mmol) was added to a stirred suspension of L-methionine methyl ester, HCl(4.37 g, 21.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The resulting mixture was left to stir for 30 min at room  
20 temperature then filtered. The filtrates were then added to a stirred solution of 3-chlorosulphonyl-benzoyl chloride (5.23 g, 21.9 mmol) and triethylamine (7.6 mL, 54.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) at 0° under argon. The reaction mixture was allowed to warm to room temperature and quenched with ice-water(100 mL). The organics were the dried over MgSO<sub>4</sub>, filtered and concentrated to a viscous brown gum. This was then purified by  
25 flash chromatography on 9385 SiO<sub>2</sub>, eluting with 50% EtOAc/i-Hexane to give (2S)-2-(3-chlorosulfonyl-benzoylamino)-4-methylsulfonyl-butyric acid methyl ester (15(a)) as a viscous orange oil: 2.88 g (36%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz) δ 2.1-2.2 (5H, m); 2.65 (2H, t); 3.83 (3H, s); 4.95 (1H, m); 7.23 (1H, d); 7.74 (1H, t); 8.2 (2H, m); 8.47 (1H, m). MS (CI) m/z 366 (M+H)<sup>+</sup>, 332, 300.

30 A solution of 15(a) (1.53 g, 4.18 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added to a stirred solution of

- 50 -

- (2S,4S)-2-aminomethyl-4-BOCsulfanyl-pyrrolidine-1-carboxylic acid allyl ester (15(b)) (prepared as described in International Patent Application WO 92/17480. see pages 39-41) (1.32g, 4.18 mmol) and (*i*Pr)<sub>2</sub>NEt (1.5 mL, 9.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30mL) at 0°C under argon. The resulting solution was allowed to warm to room temperature and stirred for 18 hours. The reaction mixture was then washed with water (100 mL), dried over MgSO<sub>4</sub>, filtered and concentrated to a viscous white gum. This was then purified by flash chromatography on 9385 SiO<sub>2</sub>, eluting with a gradient of 35-50% EtOAc/*i*-Hexane to give (2S,4S)-4-BOCsulfanyl-2-{[3-([1S]-1-methoxycarbonyl-3-methylsulfanyl-propylcarbamoyl)-benzenesulfonylamino]-methyl}-pyrrolidine-1-carboxylic acid allyl ester (15(c)) as a colourless foam: 2.19 g (81.3%).
- <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200MHz) δ 1.5 (9H, s); 1.65-1.9 (1H, s); 2.05-2.35 (5H, m); 2.4-2.7 (3H, m); 3.3-3.4 (3H, m); 3.55-3.75 (1H, m); 3.8 (3H, s); 3.9-4.2 (2H, m); 4.55 (2H, d); 4.98 (1H, m); 5.15-5.35 (2H, m); 5.8-6.0 (1H, m); 6.5 (1H, s); 7.4 (1H, s); 7.55 (1H, t); 7.9-8.05 (2H, m); 8.25 (1H, m).
- MS (FAB) *m/z* 646 (M+H)<sup>+</sup>, 590.568.546.230.
- Anal. Calcd for C<sub>27</sub>H<sub>39</sub>N<sub>3</sub>O<sub>9</sub>S<sub>3</sub>·0.3CH<sub>2</sub>Cl<sub>2</sub>: C, 48.8; H, 5.95; N, 6.26.
- Found C, 48.9; H, 6.2; N, 6.0.

- Tri-*n*Butyl tin hydride (565 mL, 2.1 mmol) was added to a stirred solution of (15(c)) (1.18 g, 1.8 mmol) and (PPh)<sub>3</sub>PdCl<sub>2</sub> (13 mg, 0.018 mmol) in a mixture of water (0.5 mL) and CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The reaction mixture was left to stir for 10 minutes, dried over MgSO<sub>4</sub>, filtered and concentrated to a brown oil. This was then purified by flash chromatography on 9385 SiO<sub>2</sub>, eluting with a gradient of 0-10% EtOAc/*i*-Hexane to give the desired starting material 15(d) as a white foam: 751 mg (73%).
- <sup>1</sup>H NMR (CDCl<sub>3</sub>+CD<sub>3</sub>COOD, 250MHz) δ 1.5 (9H, s); 1.85-1.97 (1H, m); 2.1-2.35 (5H, m); 2.45-2.7 (3H, m); 3.1-3.4 (3H, m); 3.65-4.25 (6H, m); 4.9-5.0 (1H, m); 7.63 (1H, t); 7.97-8.05 (1H, m); 8.1-8.17 (1H, m) 8.35-8.42 (1H, m).
- MS (ESP+) *m/z* 562 (M+H)<sup>+</sup>, 462.
- Anal. Calcd for C<sub>23</sub>H<sub>35</sub>N<sub>3</sub>O<sub>7</sub>S<sub>3</sub>: C, 49.2; H, 6.28; N, 7.48.
- Found C, 49.4; H, 6.3; N, 7.2.

- 51 -

Example 16 (see Scheme 16)

**(2S),2-{3-[(2S,4S)-4-sulfanyl-pyrrolidin-2-yl-methyl]-sulfamoyl}-benzoylamino}-4-methylsulfanyl-butyrlic acid**

5                2N NaOH(2.0 mL, 4.0 mmol) was added to a stirred solution of compound (15(d)) (prepared in Example 15) (200 mg, 0.36 mmol) in MeOH at room temperature under argon. After 18 h the reaction mixture was concentrated to remove the MeOH. The resulting residues were dissolved in H<sub>2</sub>O(2.0 mL) and acidified to pH3 with 2N HCl. The resulting solution was purified by reverse phase HPLC (Dynamax C18.8 $\mu$  prepcolumn).  
10 eluting with a gradient of 0-40% MeOH/H<sub>2</sub>O. Product fractions were concentrated and azeotroped with toluene (3 x 25 mL) to give a colourless glass which was then triturated with Et<sub>2</sub>O (25 mL), filtered and dried to yield the desired product 16 as a white powder: 85.2 mg (54%).

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>+CD<sub>3</sub>COOD,250 MHz)  $\delta$ 1.45-1.65 (1H, m); 2.0-2.2 (5H, m);  
15 2.3-2.7 (3H+DMSO, m); 2.95-3.2 (3H, m); 3.35-4.2 (3H, m); 4.5-4.65 (1H, m); 7.65-7.8 (1H, m); 7.9-8.05 (1H, m); 8.1-8.25 (1H, m); 8.3-8.4 (1H, m).

MS (FAB) m/z 448 (M+H)<sup>+</sup>.

Anal. Calcd for C<sub>17</sub>H<sub>25</sub>N<sub>3</sub>O<sub>5</sub>S<sub>3</sub>: C, 45.6; H, 5.63; N, 9.39.

Found C, 45.5; H, 5.8; N, 9.1.

20

Example 17 (see Scheme 17)

**N-(3,4-dichlorophenyl)-3-[(2S,4S)-4-sulfanyl-pyrrolidin-2-yl-methyl]-sulfamoyl]-benzamide**

25                N-(3,4-dichlorobenzyl)-3-[(2S,4S)-4-BOCsulfanyl-pyrrolidin-2-yl-methyl]-sulfamoyl]-benzamide (17(c)) was deprotected with TFA (analogously to compound (15(d)) in Example 15) to give the desired product 17 in 97% yield after trituration with Et<sub>2</sub>O.

<sup>1</sup>H NMR (CDCl<sub>3</sub>,200MHz)  $\delta$ 1.5-1.8 (1H, m); 1.8-2.2 (2H+H<sub>2</sub>O,m.SH.NH); 2.5-2.7  
30 (1H,m); 3.1-3.35 (3H, m); 3.4-4.1 (3H, m); 4.55 (2H, d); 7.15 (1H, dd); 7.2 (1H, s); 7.32

- 52 -

(1H, d); 7.4 (1H, d); 7.65 (1H+PPh<sub>3</sub>PO, m); 7.9 (1H, m); 8.2 (1H, m); 8.35 (1H, m); 8.5-9.3 (1H, s, NH); 10.3-10.7 (1H, s, NH).

MS (ESP+) m/z 474 (M+H)<sup>+</sup>, 279(PPh<sub>3</sub>PO)

- 5 Starting material (17(c)) was prepared as follows. 3,4-Dichlorobenzylamine was coupled with 3-Chlorosulphonylbenzoyl chloride (analogously as for compound (15(a)) in Example 15) to give

3-(3,4-dichloro-benzylcarbamoyl)-benzene-sulfonyl-chloride

(17(a)) in 28% yield.

- 10 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250MHz) δ 4.6 (2H, d); 6.6 (1H, s, NH); 7.2 (1H, dd); 7.4-7.5 (2H, m); 7.75 (1H, t); 8.15-8.25 (2H, m); 8.4 (1H, m) MS (FAB) m/z 378 (M+H)<sup>+</sup>, 380.

Compound 15(b) (Example 15) was coupled with (17(a)) analogously as for the equivalent step in Example 15 to give

- 15 N-(3,4-dichlorobenzyl)-3-[(2S,4S)-4-BOCsulfanyl-pyrrolidin-2-yl-methyl]-sulfamoyl]-benzamide (17(b)) in 72.5% yield.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200MHz) δ 1.5 (9H, s); 1.6-1.9 (1H+H<sub>2</sub>O, m); 2.4-2.6 (1H, m); 3.1-3.3 (3H, m); 3.6-3.7 (1H, m); 3.8-4.1 (2H, m); 4.4 (2H, d); 4.6 (2H, d); 5.1-5.3 (2H, m); 5.7-5.95 (1H, m); 6.08 (1H, s, NH); 7.2 (1H, dd); 7.35-7.7 (4H, m); 7.95 (1H, d); 8.15 (1H,

- 20 d); 8.25-8.35 (1H, s, NH).

MS (FAB) m/z 658 (M+H)<sup>+</sup>

Anal. Calcd for C<sub>28</sub>H<sub>33</sub>N<sub>3</sub>Cl<sub>2</sub>O<sub>7</sub>S<sub>2</sub>: C, 51.1; H, 5.05; N, 6.38.

Found C, 50.8; H, 5.2; N, 6.2.

- 25 Compound (17(b)) was deprotected, analogously as for the equivalent step in Example 15, to give the desired starting material (17(c)) in 70% yield.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 250MHz) δ 1.15-1.45 (1H, m); 1.5 (9H, s); 2.25-2.4 (1H, m); 2.6-2.9 (4H, m); 3.02 (1H, dd); 3.25-3.4 (2H, m); 3.45-3.6 (1H, m); 4.6 (2H, m); 7.05 (1H, m); 7.2 (1H, dd); 7.4 (1H, d); 7.45 (1H, d); 7.6 (1H, t); 7.95 (1H, d); 8.1 (1H, d); 8.25 (1H, s).

- 30 MS (ESP+) m/z 574 (M+H)<sup>+</sup>, 574.279 (PPh<sub>3</sub>O)

- 55 -

Example 18 (see Scheme 18)

**N-(3,4-dichlorobenzyl)-N'-([2S,4S],4-sulfanyl-pyrrolidin-2-yl-methyl)-  
isophthalamide**

5 N-(3,4-dichlorobenzyl)-N'-([2S,4S],4-BOCsulfanyl-pyrrolidin-2-yl-methyl)-isophthalamide (18(e)) was deprotected with TFA (analogously to the equivalent step in Example 15) to give the desired product 18 in 100% yield after trituration with Et<sub>2</sub>O.

<sup>1</sup>H NMR (CDCl<sub>3</sub>+CD<sub>3</sub>COOD, 250MHz) δ 1.75-1.9 (1H, m); 2.6-2.75 (1H, m); 3.2-3.35  
10 (1H, m); 3.45-3.65 (1H, m); 3.7-3.95 (3H, m); 4.05-4.15 (1H, m); 4.6 (2H, s); 7.2 (1H, dd);  
7.4 (1H, d); 7.55 (1H, t); 7.95-8.05 (1H, m); 8.1-8.2 (1H, m); 8.4 (1H, m). MS (ESP+) m/z  
438 (M+H)<sup>+</sup>.

Starting material (18(e)) was prepared as follows. A suspension of isophthalic  
15 acid monomethyl ester (18(a)), (2.65 g, 14.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and DMF (10 drops) was treated with oxalyl chloride (2.6 mL, 29.8 mmol) at 0° under argon. The reaction mixture was allowed to warm to room temperature over 18h. The resulting solution was concentrated and azeotroped with toluene to give a crystalline yellow solid. This was then redissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and added dropwise to a stirred solution of  
20 3,4-dichlorobenzylamine (2.6 g, 14.7 mmol) and Et<sub>3</sub>N (5 mL, 35.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) at 0° under argon. The resulting solution was allowed to warm to room temperature over 4 hours, washed with 1N HCl(50 mL), saturated NaHCO<sub>3</sub> (aq) (50 mL), dried over MgSO<sub>4</sub>, filtered and concentrated to an orange oil. This was then purified by flash chromatography on 9385 SiO<sub>2</sub> eluting on a gradient of 25-50% EtOAc/i-Hexane to yield  
25 3-(3,4-dichlorobenzyl-carbamoyl)-benzoic acid methyl ester (18(b)) as a pale yellow oil:  
3.99g (80%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200MHz) δ 3.9 (3H, s); 4.6 (2H, d); 6.6-6.8 (1H, t, NH); 7.18 (1H, dd);  
7.38-7.45 (2H, m); 7.54 (1H, t); 8.0-8.1 (1H, m); 8.13-8.23 (1H, m); 8.35-8.42 (1H, m). MS  
(CI) m/z 338 (M+H)<sup>+</sup>.

30

- 54 -

- A stirred solution of (18(b)) (3.85 g, 11.4 mmol) in MeOH (100 mL) at room temperature under argon was treated with 2N NaOH (12 mL, 24 mmol). The reaction mixture was allowed to stir at room temperature for 4 h, concentrated to 1/5 volume and acidified to pH4 with 2N HCl. The resulting precipitate was then collected by filtration.
- 5 washed with water (2 x 25 mL) and dried under high vacuum to yield 3-(3,4-dichlorobenzyl-carbamoyl)-benzoic acid (18(c)) as a white powder: 2.9 g (79%).
- <sup>1</sup>H NMR (DMSO-D<sub>6</sub>, 200MHz) δ4.49 (2H, d); 7.32 (1H, dd); 7.5-7.7 (3H, m); 8.0-8.2 (2H, m); 8.42-8.53 (1H, m); 9.27 (1H, t, NH); 13.0-13.4 (1H, s, COOH).
- MS (ESP+) m/z 324 (M+H)<sup>+</sup>, 159.
- 10 Anal. Calcd for C<sub>15</sub>H<sub>11</sub>NO<sub>3</sub>Cl<sub>2</sub>·0.4H<sub>2</sub>O C, 54.4; H, 3.59; N, 4.23  
Found C, 54.0; H, 3.2; N, 4.2

- 1-(3-Dimethylaminopropyl)-3-ethyl carbodiimide.HCl (655 mg, 3.4 mmol) and 1-Hydroxybenztriazole (463 mg, 3.4 mmol) were added portionwise to a stirred
- 15 solution of (18(c)) (1.0 g, 3.1 mmol) in DMF (20 mL) at 0° under argon. After 30 mins a solution of compound (15(b)) (Example 15) (1.13 g, 3.57 mmol) in DMF (20 mL) was added dropwise, followed by N-methyl morpholine (375 ml, 3.4 mmol). The mixture was then allowed to warm to room temperature over 4 hours. The resulting reaction mixture was concentrated to 1/5 volume and diluted with EtOAc(100 mL). This solution was then
- 20 washed successively with 1N citric acid (100 mL), saturated NaHCO<sub>3</sub>(aq) (100 mL), water (100 mL) and brine (100 mL), dried over MgSO<sub>4</sub>, filtered and concentrated to a white foam. This was then purified by flash chromatography on 9385 SiO<sub>2</sub>, eluting on a gradient of 50-75% EtOAc/i-Hexane to yield (2S,4S)-4-BOCsulfanyl-2-  
{[3-(3,4-dichlorobenzylcarbamoyl)-benzoylamino]-methyl}-pyrrolidine-1-carboxylic acid
- 25 allyl ester (18(d)) as a white foam: 1.57 g (82%).
- <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250MHz) δ1.5 (9H, s); 1.6-1.9 (1H, m); 2.55-2.75 (1H, m); 3.2-3.6 (2H,m); 3.65-3.9 (2H, m); 4.1-4.25 (2H, m); 4.5-4.65 (4H, m); 5.15-5.35 (2H, m); 5.38-6.0 (1H, m); 6.87 (1H, t, NH); 7.2 (1H, dd); 7.4 (1H, d); 7.45 (1H, d); 7.55 (1H, t); 7.95 (1H, d); 8.07 (1H, d); 8.25 (1H, s); 8.35-8.6 (1H, s, NH).
- 30 MS (ESP+) m/z 622 (M+H)<sup>+</sup>, 566, 522.
- Anal. Calcd for C<sub>29</sub>H<sub>33</sub>N<sub>3</sub>Cl<sub>2</sub>O<sub>6</sub>S : C, 55.9; H, 5.34; N, 6.75

SUBSTITUTE SHEET (RULE 26)



- 55 -

Found C. 56.1; H. 5.6; N. 6.6

Compound (18(d)) was deprotected (analogously as for the equivalent step in Example 15) to give the desired starting material (18(e)) in 67% yield.

- 5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200MHz)  $\delta$  1.2-1.6 (10H, m); 2.25-2.55 (2H, m) 1H + 1NH); 2.9 (1H, q); 3.3-3.75 (5H, m); 4.6 (2H, d); 6.9-7.05 (1H, m, NH); 7.05-7.15 (1H, m, NH); 7.2 (1H, dd); 7.4 (1H, d); 7.45 (1H, d); 7.52 (1H, t); 7.9-8.05 (2H, m); 8.23 (1H, m).  
MS (ESP+)  $m/z$  538 (M+H) $^+$ , 438.

10 Example 19 (see Scheme 19)

**(2S,4S)-4-sulfanyl-2-[(3-methoxycarbonyl-benzoylamino)-methyl]-pyrrolidin-1-carboxylic acid allyl ester**

- (2S,4S)-4-BOCsulfanyl-2-[(3-methoxycarbonyl-benzoylamino)-methyl]-pyrrolidin-1-carboxylic acid allyl ester (19(a)), (300 mg, 0.63 mmol) was dissolved in TFA (5 mL) at room temperature under argon. The reaction mixture was concentrated and azeotroped with toluene (3 x 20 mL) to yield the desired product (19) as a colourless viscous gum: 250 mg (105%).

- 15  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200MHz)  $\delta$  1.6-1.85 (2H, m, CH+SH); 2.55-2.85 (2H, m); 3.1-3.6 (3H, m); 3.92 (3H, bs); 4.0-4.4 (2H, m); 4.65 (2H, d); 5.15-5.4 (2H, m); 5.8-6.1 (1H, m); 7.53 (1H, t); 8.0-8.1 (1H, m); 8.1-8.25 (1H, m); 8.3-8.7 (2H, m, Aromatic-H + NH).  
20 MS (FAB)  $m/z$  379 (M+H) $^+$ , 163.

- 25 Starting material (19(a)) was prepared as follows. A suspension of isophthalic acid monomethyl ester (compound 18(a), Example 18), (2.5 g, 13.89 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) and DMF (10 drops) was treated with oxalyl chloride (1.35 mL, 15.5 mmol) at 0 $^\circ$  under argon. The reaction mixture was allowed to warm to room temperature over 18 h. The resulting solution was concentrated and azeotroped with toluene to give a crystalline  
30 yellow solid. This was then redissolved in  $\text{CH}_2\text{Cl}_2$  (50 mL) and added dropwise to a stirred solution of (2S,4S)-2-aminomethyl-4-BOCsulfanyl-pyrrolidine-1-carboxylic acid

SUBSTITUTE SHEET (RULE 26)

- 56 -

allyl ester (compound 15(b), Example 15) (2.0 g, 6.33 mmol) and (iPr)<sub>2</sub>NEt (2.2 mL, 12.66 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) at 0° under argon. The reaction mixture was allowed to warm to room temperature and stirred for 18 hours, then washed with water (2 x 50 mL), dried over MgSO<sub>4</sub>, filtered and concentrated to a dark brown oil. This was then purified by flash chromatography on 9385 SiO<sub>2</sub> eluting with a gradient of 25-50%EtOAc/i-Hexane to yield the desired starting material (19(a)) as a pale yellow, viscous oil: 1.81 g (60%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200MHz) δ 1.5 (9H, s); 1.65-1.9 (1H, m); 2.55-2.8 (1H, m); 3.3 (1H, q); 3.4-3.65 (1H, m); 3.65-3.9 (2H, m); 3.95 (3H, s); 4.05-4.35 (2H, m); 4.6-4.7 (2H, m); 5.15-5.4 (2H, m); 5.8-6.1 (1H, m); 7.52 (1H, t); 8.02 (1H, dd); 8.15 (1H, dd); 8.25-8.5 (1H, bs, NH);

8.55 (1H, bs). MS (FAB) m/z 479 (M+H)<sup>+</sup>, 423.163.

Anal. Calcd for C<sub>23</sub>H<sub>30</sub>N<sub>2</sub>O<sub>7</sub>S : C, 57.7; H, 6.32; N, 5.85.

Found C, 57.5; H, 6.4; N, 5.7.

15 Example 20 (see Scheme 20)

**N-([2S,4S],4-sulfanyl-pyrrolidin-2-yl-methyl)-3-phenoxy-benzamide**

3-Phenoxybenzoic acid was coupled with (2S,4S)-2-aminomethyl-4-BOCsulfanyl-pyrrolidine-1-carboxylic acid allyl ester (compound (15(b)), Example 15), followed by selective deprotection of the N-allyloxycarbonyl group and removal of the BOC group (analogously to the equivalent steps in Example 15) to give the desired product 20.

NMR CDCl<sub>3</sub> δ 1.8 (1H, m), 2.72 (1H, m), 3.01-3.31 (1H, bd), 3.69-3.97 (4H, m), 4.3 (1H, bs), 6.92-7.17 (4.5H, m, aromatics), 7.23-7.45 (5.5H, m, aromatics), 7.56 (1H, m), 7.68 (1H, t), 8.02-8.29 (1H, 2t), 9.02-9.29 (1H, 2bs). +ether.

Analysis requires for C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>S.HI C=47.33, H=4.6, N=6.13; Found C=47.8, H=4.5, N=6.1

30

- 57 -

Example 21 (see Scheme 21)

**5-([2S,4S],1-allyloxycarbonyl-4-sulfanyl-pyrrolidin-2-yl-methyl)-  
carbamoyl}-isophthalic acid dimethyl ester**

5 Benzene-1,3,5-tricarboxylic acid dimethyl ester was coupled to  
(2S,4S)-2-aminomethyl-4-BOCsulfanyl-pyrrolidine-1-carboxylic acid allyl ester  
(compound (15(b)), Example 15), followed by removal of the BOC group (analogously to  
the equivalent steps in Example 15) to give the desired product 21.

NMR CDCl<sub>3</sub> δ 1.67 (1H, m), 1.75 (1H, d), 2.66-2.89 (3H, m), 3.21  
10 (1H, q), 3.27-3.37 (1H, m), 3.5 (1H, m), 3.9 (2H, bs), 3.97 (6H, s), 4.08-4.27 (2H, m), 4.68  
(2H, d), 5.2-5.4 (2H, m), 5.88-6.06 (1H, m), 8.68 (2H, bs), 8.8 (1H, d).

Analysis requires for C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>7</sub>S C = 55.0 H = 5.54 N = 6.42: Found C = 54.9 H =  
5.6 N = 5.75

15 Example 22 (see Scheme 22)

**(2S)-2-{3-[(2S,4S)-4-sulfanyl-pyrrolidin-2-yl-methyl]-amino}-benzoyl-amino}-4-  
methylsulfanyl-butyric acid methyl ester**

(2S)-2-{3-[(2S,4S)-4-BOCsulfanyl-pyrrolidin-2-yl-methyl]-amino}-  
20 benzoylamino}-4-methylsulfanyl-butyric acid methyl ester (22g) was deprotected  
(analogously as for the equivalent step in Example 15) to yield the desired end product  
(22).

<sup>1</sup>H NMR (CDCl<sub>3</sub>+CD<sub>3</sub>COOD) δ 1.7-1.9 (1H, m); 2.0-2.4 (6H+CH<sub>3</sub>COOH, M); 2.5-2.8 (3H, M);  
3.23 (1H, Q); 3.45-3.7 (2H, m); 3.7-3.9 (4H, m); 3.95-4.15 (1H, m); 4.8-4.95 (1H, m); 6.8 (1H, d); 7.0  
25 5-7.18 (2H, m); 7.23 (1H, t).

MS (ESP) m/z 398 (M+H)<sup>+</sup>, 235.

Anal. Calcd for C<sub>18</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub>S<sub>2</sub>1.25TFA: C, 45.6; H, 5.27; N, 7.78

Found C, 45.2; H, 5.3; N, 7.4

30 Starting material 22g was prepared as follows.

SUBSTITUTE SHEET (RULE 26)

- 58 -

i) Preparation of (2S,4S)-4-BOCsulfanyl-2-formyl-pyrrolidine-1-carboxylic acid allyl ester (22b)

TPAP (5.5mg,0.0156mmol) was added to a stirred mixture of

5 (2S,4S)-4-BOCsulfanyl-2-hydroxymethyl-pyrrolidine-1-carboxylic acid allyl ester (22a)(100mg,0.31mmol) and NMM-O (56mg,0.478mmol) in CH<sub>2</sub>Cl<sub>2</sub>(2.0mL) and CH<sub>3</sub>CN (100μL) containing dried powdered 4A° molecular sieve(200mg). The reaction mixture was left to stir for 1h then concentrated to dryness. This was then purified by flash chromatography on SiO<sub>2</sub> (Varian Mega Bond Elut Column) eluting with 50%

10 EtOAc/i-Hexane to give compound 22b as a colourless gum: 66.3mg(66.7%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>,250MHZ) δ1.4-1.6(9H.m);2.0-2.25(1H.m);2.45-2.75(1H.m); 3.45-3.6(1H.m);3.75-3.9(1H.m);3.9-4.1(1H.m);4.1-4.35(1H.m);4.5-4.7(2H.m);5.15-5.4(2H.m);5.75-6.05(1H.m);9.4(1H.s.CHO).

MS (CI) m/z 316 (M+H)<sup>+</sup>.260.216.

15

ii) Preparation of

(2S)-2-[(3-amino-benzoyl)-amino]-4-methylsulfanyl-butyric acid methyl ester (22e)

3-Nitro-benzoic acid (22c)(2.0g,11.9mmol) was coupled with L-methionine methyl ester hydrochloride (2.6g,13mmol) according to the method used to synthesise compound 18a. to give

(2S)-2-[(3-nitro-benzoyl)-amino]-4-methylsulfanyl-butyric acid methyl ester (22d) as a white solid:3.15g(93.4%)

<sup>1</sup>H NMR (CDCl<sub>3</sub>,200MHZ)Δ2.05-2.45(5H.m);2.63(2H,t);3.82(3H.s);4.96(1H,m); 25 7.2(1H.d.NH);7.65,1H.t);8.18(1H.m);8.39(1H.m);8.65(1H,m).

MS (ESP) m/z 313 (M+H)<sup>+</sup>.265.253.

Anal. Calcd for C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub>S:C.50.0;H.5.16;N.8.97

Found C,50.3;H,5.1;N.8.9

30 A stirred solution of 22d (500mg,1.62mmol) in MeOH(10mL) was treated portionwise with decolourising charcoal (50mg). and iron III chloride hexahydrate

**SUBSTITUTE SHEET (RULE 26)**

- 59 -

- (7mg, 0.026mmol). *N,N*-Dimethyl hydrazine (1.5mL, 19.8mmol) was then added dropwise and the resulting suspension was heated to reflux for a total of 18h. The reaction mixture was then concentrated to dryness and the residues purified by flash chromatography on SiO<sub>2</sub> (Varian Mega Bond Elut Column) eluting with 50%EtOAc/i-Hexane. Product
- 5 fractions were then concentrated to yield a colourless oil which crystallised on standing. This was then triturated with Et<sub>2</sub>O to give 22e as a white powder which was collected by filtration and dried: 367mg (81.2%)
- <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250MHz) δ 2.0-2.4(5H.m); 2.5-2.65(2H.m); 3.8(3H.s); 4.9(1H.m); 6.75-6.95(2H.m.ArH+CONH); 7.05-7.3(3H.m).
- 10 MS (ESP) m/z 283 (M+H)<sup>+</sup>, 251, 235, 223.
- Anal. Calcd for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>S: C.55.3; H.6.43; N.9.92
- Found C.55.5; H.6.6; N.9.8

## iii) Preparation of 22g

- 15 A solution containing 22e (50mg, 0.17mmol) and 22b (54mg, 0.17mmol) in EtOH(2.5mL) was treated with powdered 4A° molecular sieves (100mg) and the resulting suspension was stirred at room temperature for 1h. Acetic acid (10μL) and sodium
- cyanoborohydride (17mg, 0.27mmol) were then added and the reaction mixture was left to stir for 18h at room temperature. The reaction mixture was then partitioned between
- 20 EtOAc(50mL) and saturated NaHCO<sub>3</sub>(aq)(50mL). The aqueous phase was then washed with EtOAc(50mL) and the combined organics dried over MgSO<sub>4</sub>, filtered and concentrated to a colourless gum. This was then purified by flash chromatography on SiO<sub>2</sub> (Varian Mega Bond Elut Column) eluting a gradient of 25-40% EtOAc/i-Hexane to give
- 25 (2S)-2-{3-[[[2S,4S]-1-allyloxycarbonyl-4-BOCsulfanyl-pyrrolidin-2-yl-methyl]-amino]-benzoyl-amino}-4-methylsulfanyl-butyric acid methyl ester (22f) as a colourless gum: 60.1mg (60.3%).
- <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200MHz) δ 1.45(9H.s.<sup>t</sup>Bu); 1.7-1.9(1H.m); 2.0-2.4(5H.m); 2.45-2.7(3H.m); 3.1-3.35(2H.m); 3.4-3.6(1H.m); 3.6-3.85(4H.m); 4.0-4.3(2H.m);
- 30 4.6(2H.m); 4.8-4.95 (1H.m); 5.15-5.4(2H.m); 5.8-6.1(1H.m); 6.75(1H,d); 6.5-7.3(5H.m).
- MS (ESP) m/z 582 (M+H)<sup>+</sup>, 482.

SUBSTITUTE SHEET (RULE 26)

- 60 -

Compound 22f was deprotected (analogously as for the equivalent step in Example 15) to give the desired starting material 22g in 64% yield.

$^1\text{H}$  NMR ( $\text{CDCl}_3 + \text{D}_2\text{O}$ )  $\delta$  1.15-1.95 (10H, m); 1.95-2.15(4H, m, SMe+H);

2.15-2.35(1H, m); 2.35-2.5(1H, m); 2.55(2H, t); 2.75-2.95(1H, m); 2.95-3.15(1H, m);

5 3.15-3.55(3H, m); 3.55-3.7(1H, m); 3.78(3H, s, COMe); 4.9(1H, m); 6.73(1H, m);

6.98-7.13(2H, m); 7.2(1H, t).

MS (ESP)  $m/z$  498 ( $\text{M} + \text{H}$ ) $^+$ . 398.

Anal. Calcd for  $\text{C}_{23}\text{H}_{35}\text{N}_3\text{O}_5\text{S}_2\text{O} \cdot 0.35\text{CH}_2\text{Cl}_2$ : C.53.2; H.6.82; N.7.97

Found C.53.5; H.7.1; N.7.5

10

Example 23 (see Scheme 30)

#### Preparation of

N-((2S,4S)-4-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-N-(2-naphthalen-1-yl-ethyl)butyramide (compound 9);

15 (2S,4S)-2-[[ (3-Methoxypropyl)-(2-naphthalen-1-ylethyl)amino]methyl]-pyrrolidine-4-thiol (compound 10) and:

(2S,4S)-2-[[ (2-(4-Methoxyphenyl)methyl)-(2-naphthalen-1-ylethyl)amino]methyl]-pyrrolidine-4-thiol (compound 11).

#### 20 Preparation of Compound 9

A solution of starting material N-((2S,4S)-4-BOCsulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-N-(2-naphthalen-1-yl-ethyl)butyramide (6) (770 mg) in trifluoroacetic acid (40ml) was stirred at ambient temperature for 10 minutes. The trifluoroacetic acid was evaporated under reduced pressure and the residue redissolved in diethyl ether (90 ml). Ethereal

25 HCl(1M .10ml) was added and the resulting suspension centrifuged. The diethyl ether was decanted off and more ether(90ml) added to the residue. This mixture was stirred for five minutes and then recentrifuged. The washing/centrifuging procedure was repeated once more and the resulting white solid dried under reduced pressure to give compound (9). (600mg)

30 NMR. data in  $\text{DMSO}-d_6$   $\delta$  0.6(2d, 6H), 0.95(d, 1H), 1.7(m, 3H), 2.15(m, 1H), 1.9(m, 1H), 3.0 to 3.85(m, 10h), 7.3 to 8.4(m, 7H), 8.9(br.s, 1H), 9.5(br.s, 1H).

SUBSTITUTE SHEET (RULE 26)

- 61 -

Micro Analysis:            %Theory C64.9. H7.7. N6.9  
(1.00 HCl )                %Found C64.7. H7.9. N6.8

Starting material (6) was prepared as follows.

- 5 (2S,4S)-2-Formyl-4-BOCsulfanyl-pyrrolidine-1-carboxylic acid allyl ester (1) (1.84 g) in dichloromethane(20ml) was added dropwise over 10 minutes to a mixture of 2-naphthalen-1-ylethylamine (1.0g), sodium triacetoxyborohydride(1.36g) and 4A powdered molecular sieve (3.0 g) in dichloromethane (130ml) cooled to -20°C. and stirred under an argon atmosphere. After the addition was complete the reaction was allowed to warm to
- 10 ambient temperature and stirred for a further 18 hours. The molecular sieves were filtered off and the filtrate stirred with saturated aqueous sodium bicarbonate solution(100 ml) for 5 minutes. The mixture was separated, the organic phase dried over magnesium sulphate and applied to a silica flash column which was then eluted with 1.Ethyl acetate/Hexane(50:50), 2.Ethyl acetate/Hexane(80/20), 3.Ethyl acetate to give (2S,4S)-4-BOCsulfanyl-2[(2-
- 15 naphthalen-1-ylethylamino)-methyl]pyrrolidine-1-carboxylic acid allyl ester (2) (2.2 g) as a colourless gum.

NMR data in CDCl<sub>3</sub>, δ 1.5(s, 9H), 1.85(m, 1H), 2.5(m, 1H), 2.8(m, 1H), 3.0(m, 3H), 3.2(m, 3H), 3.7(m, 1H), 4.05(m, 2H), 4.55(d, 2H), 5.25(m, 2H), 5.9(m, 1H), 7.43(m, 4H), 7.7(d, 1H), 7.83(m, 1H), 8.05(m, 1H).

20

A mixture of compound (2)(1.2g), isovaleryl chloride(0.61g) and triethylamine(0.77g) in dichloromethane(75ml) was stirred for 1 hour at ambient temperature. The reaction mixture was then applied to a silica flash column which was eluted with ethyl acetate/hexane(20:80) to give compound(3) as a colourless gum (1.3g).

25

- Tributyltin hydride(6.46g) was added dropwise over 5 minutes to a stirred mixture of compound(3)(1.23g) and bis(triphenylphosphine)palladium(0) chloride(20 mg) in dichloromethane(75ml). This mixture was stirred at ambient temperature for 30 minutes and then applied to a silica flash column which was eluted with 1.Ethyl acetate/Hexane(50:50), 2.Ethyl acetate, 3.Ethyl acetate/Methanol(95:5). The product
- 30 obtained was recoloured on an Isolute® C18(10g) column eluting with

SUBSTITUTE SHEET (RULE 26)

- 62 -

methanol/water(80:20) to give starting material compound (6) as a white solid (769 mg), m.pt. 86°.

NMR data (CDCl<sub>3</sub>) δ 0.9(2d, 6H), 1.3(m, 1H), 1.5(s, 9H), 1.8-2.5(m, 6H), 2.9(m, 1H),  
5 3.05-3.9(m, 9H), 7.25-8.35(m, 7H).

#### Preparation of Compound(10)

A solution of starting material (2S,4S)-2-{[(3-methoxypropyl)-(2-naphthalen-1-  
10 ylethyl)amino]methyl}-pyrrolidine-4-BOCthiol (compound 7) (78 mg) in trifluoroacetic acid(5 ml) was stirred at ambient temperature for 30 minutes. The trifluoroacetic acid was removed under reduced pressure and the residue treated with diethyl ether(5 ml). The ether was decanted off and the residue dried under reduced pressure for 24 hours to give the desired end product as a colourless gum (compound10)(70 mg).

15

NMR data (CDCl<sub>3</sub>) δ 1.95(m, 4H), 2.05(m, 1H), 3.16-3.62(m, 10H), 3.29(s, 3H), 3.7(m, 1H), 4.15(m, 2H), 7.3-7.65(m, 4H), 7.68((d, 1H), 7.88(d, 1H), 7.98(d, 1H), 11.2(br.s, 2H).

Micro Analysis:	%Theory C48.2, H5.13, N4.32
20 (2.5TFA, 0.25H <sub>2</sub> O)	%Found C48.5, H5.20, N4.40

Starting material (compound 7) was prepared as follows.

A solution of 4-methoxy-butyraldehyde(140mg) in dichloromethane(10 ml) was added  
25 dropwise to a mixture of compound (2)(250 mg), sodium triacetoxymethylborohydride(338 mg) and 4A molecular sieves(1.0 g) in dichloromethane(30 ml) stirred under an argon atmosphere at -20°. After the addition was completed (5 minutes) the reaction mixture was allowed to warm to ambient temperature and stirred for 18 hours. The molecular sieves were filtered off and the filtrate washed with saturated sodium bicarbonate solution(20 ml).  
30 then brine and dried over magnesium sulphate. The solution was then applied to a silica

SUBSTITUTE SHEET (RULE 26)



- 63 -

column and eluted with ethyl acetate/hexane(50:50) to give a clear gum, compound(4)(260 mg).

Compound(7) was synthesised from compound(4) analogously to the preparation of compound(6).

NMR data (CDCl<sub>3</sub>) δ 1.35(m, 1H), 1.48(s, 9H), 1.74(m, 2H), 2.31(m, 1H), 2.42-3.1(m, 7H), 3.15-3.5(m, 9H), 3.65(m, 1H), 7.28-8.1(m, 7H).

#### Preparation of Compound(11)

10

Compound(11) was synthesised from starting material (2*S*,4*S*)-2-{[(2-(4-methoxyphenyl)methyl)-(2-naphthalen-1-ylethyl)amino]methyl}-pyrrolidine-4-BOCthiol (compound 8) by the method described for the equivalent step in preparation of compound(10).

15

NMR data (CDCl<sub>3</sub>) δ 1.9(m, 1H), 2.05(m, 1H), 2.3(m, 1H), 3.1-3.8(m, 8H), 3.82(s, 3H), 4.25(m, 3H), 6.96(d, 2H), 7.42(m, 6H), 7.83(m, 3H).

Micro Analysis:	%Theory	C55.7, H5.77, N4.06
20 (2TFA, 0.75diethyl ether)	%Found	C56.0, H5.40, N4.50

The starting material for compound(11) was prepared as follows:

A mixture of compound(2) (200mg), *p*-methoxybenzyl chloride(133 mg), saturated aqueous sodium bicarbonate(5ml) and dichloromethane(20ml) was stirred at ambient temperature for 24 hours. The layers were separated and the organic layer dried, applied to a silica flash column which was then eluted with ethyl acetate/hexane(80:20) to give (2*S*,4*S*)-1-allyloxycarbonyl-2-{[(2-(4-methoxyphenyl)methyl)-(2-naphthalen-1-ylethyl)amino]methyl}-pyrrolidine-4-BOCthiol compound(5) as a colourless gum(140 mg).

- 64 -

NMR data (CDCl<sub>3</sub>) δ 1.45(s, 9H), 2.0(m, 1H), 2.35(m, 1H), 2.53-4.15(m, 10H), 3.8(s, 3H), 4.6(m, 4H), 5.25(m, 2H), 5.9(m, 1H), 6.85(m, 3H), 7.3(m, 6H), 7.75(m, 2H).

The desired starting material (compound(8)) was synthesised from compound(5) by the same procedure used to prepare compound(6) from compound (3).

Mass Spec.(ESP+) m/e 507.0

Example 24 (see Scheme 31)

#### Preparation of

- 10 a) **3-Methyl-N-(naphthalen-1-ylmethyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-butanamide** (compound 23);
- b) **N-(naphthalen-1-ylmethyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-pentanamide** (compound 24);
- c) **N-(naphthalen-1-ylmethyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-2-(pyridin-3-yl)-acetamide** (compound 27);
- 15 d) **3-Methyl-N-(naphthalen-1-ylmethyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-pentanamide** (compound 25);
- e) **3-Methoxy-N-(naphthalen-1-ylmethyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-propanamide** (compound 26) and;
- 20 f) **(2S,4S)-2-[{N-(4-methoxybenzyl)-N-(naphthalen-1-ylmethyl)-amino}-methyl]-pyrrolidine-4-thiol** (compound 54).

#### a) Preparation of Compound 23

- A solution of starting material 3-methyl-N-(naphthalen-1-ylmethyl)-N-([2S,4S]-4-BOCsulfanyl- pyrrolidin-2-ylmethyl)-butanamide (compound(18)) (187mg) in
- 25 trifluoroacetic acid (10ml) was stirred at ambient temperature for 5 minutes. The trifluoroacetic acid was evaporated under reduced pressure and the resulting residue was redissolved in ethyl acetate (5ml). A solution of hydrogen chloride (2ml/1.0M) was added to the solution followed by diethylether (5ml). The mixture was centrifuged, the solvent
- 30 decanted off and the residue was washed with more diethylether (2x15ml) and dried to give the hydrochloride salt of compound(23) as an off-white solid (43mg).

SUBSTITUTE SHEET (RULE 26)

- 65 -

N.M.R. data (DMSO-d<sub>6</sub>)  $\delta$  0.83 (m,6H), 0.95(d,1H), 1.68(m,1H), 2.10(m,3H),  
2.42(m,1H), 3.10(m,1H), 3.28-3.90(m,5H), 5.20(m,2H), 7.08(d,1H), 7.57(m,3H),  
7.87(d,1H), 8.00(m,2H), 9.10-9.80(2br.s,2H)

5

Micro Analysis :	Theory %	C62.7, H7.52, N6.97
(1HCl.0.5H <sub>2</sub> O)	Found %	C62.4, H7.6, N6.7

The starting material compound(18) was prepared as follows.

10

A solution of (2S,4S)-2-formyl-4-BOCsulfanyl- pyrrolidine-1-carboxylic acid allyl ester (compound (1)) (3.11gm. ) in dichloromethane(60 ml.) was added dropwise to a stirred mixture of 1-naphthalenemethylamine (1.71g), 4A molecular sieves(12grms) and sodium triacetoxyborohydride(2.3grms) in dichloromethane (200ml) under an argon  
15 atmosphere at -20°. The mixture was stirred for a further 30 minutes at -20°C and then allowed to warm to ambient temperature and stirred for a further 16 hours. The mixture was filtered and washed with aqueous sodium bicarbonate solution (2x200ml), the organic phase further washed with water (200ml), separated, dried over magnesium sulphate and purified by column chromatography, using ethyl acetate/hexane (30:70) as eluent to give  
20 (2S,4S)-2- {[naphthalen-1-ylmethyl]-amino)-methyl}-4-BOCsulfanyl- pyrrolidine-1-carboxylic acid allyl ester (compound(12)) as a pale yellow oil (2.09g).

N.M.R. data (CDCl<sub>3</sub>)  $\delta$  1.50(s,9H), 1.55(m,1H), 1.90(m,1H), 2.50(m,1H), 2.90(m,1H),  
3.05(m,1H), 3.20(m,1H), 3.68(m,1H), 4.08(m,2H), 4.23(s,2H), 4.55(d,2H), 5.20(m,2H),  
25 5.90(m,1H), 7.47(m,4H), 7.77(m,1H), 7.86(m,1H), 8.13(m,1H).

A mixture of compound(12) (507mg), triethylamine(0.3 ml) and isovaleryl chloride(0.271ml) in dichloromethane (30ml) was stirred at ambient temperature for 1.5 hours and then applied directly to a silica flash column. This was eluted with ethyl  
30 acetate/hexane (25:75) and ethylacetate/hexane(35:65) to give 3-Methyl-N-(naphthalen-1-

- 66 -

ylmethyl)-N-([2S,4S]-1-allyloxycarbonyl-4-BOCsulfanylpyrrolidin-2-ylmethyl)-butanamide (compound(13)) as a gum (475mg).

N.M.R. data (DMSO-d<sub>6</sub>, 373°K)  $\delta$  0.90(m,6H), 1.45(s,9H), 1.78(m,1H), 2.18(m,3H),  
5 2.50(m,1H), 3.15(q,1H), 3.45(m,1H), 3.70(m,2H), 4.03(q,1H), 4.20(m,1H), 4.45(m,2H),  
5.10(m,4H), 5.80(m,1H), 7.20(d,1H), 7.50(m,3H), 7.80(d,1H), 7.92(m,1H), 8.00(m,1H).

Tributyltin hydride(2.22 ml) was added dropwise to a mixture of compound(13) (446 mg),  
bis-triphenylphosphine palladium chloride(5.8 mg) in dichloromethane (10ml). The  
10 mixture was stirred at ambient temperature under an argon atmosphere for 70 minutes and  
then applied directly to a flash column which was eluted with (1)Ethyl acetate/hexane  
(50:50) and (2) Ethyl acetate. The product obtained was recolumned on an Isolute® C18  
(10g) column, eluting with methanol/water (1) (70:30), (2)(75:25) and (3)(80:20) to give  
the desired starting material (compound(18)) as a gum (197mg).

15

N.M.R. data (DMSO-d<sub>6</sub>, 373°K)  $\delta$  0.90(m,6H), 1.45(m,5H), 1.60(m,1H), 1.68(m,2H),  
2.12(m,2H), 2.25(d,2H), 2.40(m,1H), 2.60-3.85(m,8H), 5.14(s,2H), 7.20(d,1H),  
7.50(m,3H), 7.83(m,1H), 7.93(m,1H), 8.03(m,1H).

20 b) Preparation of Compound 24

Compound(24) was synthesised by the same procedure used for compound(23) but  
substituting appropriate compounds as indicated in Scheme 31.

Compound 24:

N.M.R. data (DMSO-d<sub>6</sub>)  $\delta$  0.85(m,3H), 1.15-1.75(m,5H), 2.28(t,2H), 3.10(m,1H), 3.33-  
25 3.95(m,6H), 5.18(m,2H), 7.20(2d,1H), 7.55(m,3H), 7.85(d,1H), 8.00(m,2H), 8.95-  
9.90(2br.s,2H)

Micro Analysis :	%Theory C62.7, H7.52, N6.97
(1HCl, 0.5H <sub>2</sub> O)	%Found C62.5, H7.80, N6.8

30

- 67 -

Compound(14):

N.M.R. data (CDCl<sub>3</sub>)  $\delta$  0.90(m.3H), 1.12-2.10(m.6H), 1.48(s.9H), 2.26(m.1H), 2.50(m.1H), 3.00-5.70(m.12H), 5.87(m.1H), 7.07-8.06(m.7H).

5 Compound(19):

N.M.R. data (DMSO-d<sub>6</sub>, 373°K)  $\delta$  0.84(m.3H), 1.30(m.3H), 1.45(s.9H), 1.55(m.2H), 2.34(m.3H), 2.80(m.2H), 3.45(m.5H), 5.10(m.2H), 7.25(d.1H), 7.50(m.3H), 7.80(d.1H), 7.90(m.1H), 8.03(m.1H).

10 c) Preparation of Compound(27)

Compound(27) was synthesised, in the same manner as the equivalent step for compound(23), from starting material N-(naphthalen-1-ylmethyl)-N-([2S,4S]-4-BOCsulfanylpyrrolidin-2-ylmethyl)-2-(pyridin-3-yl)-acetamide (compound(22)).

15 Compound(27):

N.M.R. data (DMSO-d<sub>6</sub>)  $\delta$  1.70(m.1H), 2.50(m.1H), 3.14(m.1H), 3.28-5.10(m.7H), 5.35(m.2H), 7.20-9.00(m.11H), 9.20(br.s, 1H), 10.05-10.50(2br.s, 1H)

Micro Analysis : %Theory C55.10, H6.60, N7.97

(2HCl.2.25H<sub>2</sub>O, 0.3 diethyl ether) %Found C54.80, H6.10, N7.60

20

Starting material (compound(22)) was synthesised as follows.

A mixture of compound(12)(345mg), 4-dimethylamino-pyridine(305mg), 3-pyridylacetic acid hydrochloride(262mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride(348mg) in dichloromethane (30ml) was stirred at ambient temperature.

25 under an argon atmosphere, for 16hours. The mixture was then purified by silica flash column chromatography, eluting with ethyl acetate/hexane(75:25) and then ethyl acetate to give N-(naphthalen-1-ylmethyl)-N-([2S,4S]-1-allyloxycarbonyl-4-BOCsulfanylpyrrolidin-2-ylmethyl)-2-(pyridin-3-yl)-acetamide (compound(17)) as a colourless gum (394mg).

30

- 68 -

Compound(17):

N.M.R. data (DMSO-d<sub>6</sub>, 373°K)  $\delta$  1.46(s,9H), 1.75(m,1H), 2.50(m,1H), 3.17(q,1H), 3.50(m,1H), 3.75(m,4H), 4.04(m,1H), 4.27(m,1H), 4.45(m,2H), 5.15(m,4H), 5.83(m,1H), 7.25(m,2H), 7.43(t,1H), 7.52(m,2H), 7.58(m,1H), 7.82(d,1H), 7.95(m,2H), 8.40(d,2H).

5

Using the procedure previously described for the equivalent step in synthesis of compound 23, the desired starting material (compound(22)) was synthesised from compound(17).

Compound(22)

10 N.M.R. data (DMSO-d<sub>6</sub>, 373°K)  $\delta$  1.45(s,9H), 2.38(m,1H), 2.55-4.00(m,10H), 5.20(m,2H), 7.25(m,2H), 7.50(m,4H), 7.90(m,3H), 8.40(m,2H).

d) Preparation of Compound(25)

15 Compound(25) was synthesised using compounds 12, 15 and 20 as intermediates, in the same manner as the equivalent steps for synthesis of compound (27) (see Scheme 31).

Compound(25):

N.M.R. data (DMSO-d<sub>6</sub>)  $\delta$  0.80(m,6H), 0.95-4.80(m,14H), 5.18(m,2H), 7.08(d,1H), 7.55(m,3H), 7.95(m,3H), 8.90-10.15(2br.d,2H).

20

Micro Analysis : %Theory C59.1, H7.30, N6.27

(2HCl. 0.2H<sub>2</sub>O) %Found C59.1, H6.90, N5.9

Compound(15):

25 N.M.R. data (DMSO-d<sub>6</sub>, 373°K)  $\delta$  0.85(m,6H), 1.15(m,1H), 1.35(m,1H), 1.45(s,9H), 1.75(m,1H), 1.90(m,1H), 2.17(m,1H), 2.30(m,1H), 2.50(m,1H), 3.15(q,1H), 3.45(m,1H), 3.70(m,2H), 4.03(q,1H), 4.20(m,1H), 4.44(d,2H), 5.10(m,4H), 5.80(m,1H), 7.20(d,1H), 7.50(m,3H), 7.80(d,1H), 7.90(m,1H), 8.00(m,1H).

30

- 69 -

Compound(20):

N.M.R. data (DMSO-d<sub>6</sub>, 373°K)  $\delta$  0.85(m.6H), 1.25(m.3H), 1.45(s.9H), 1.93(m.1H), 2.27(m.3H), 3.40(m.6H), 5.13(m.2H), 7.25(d.1H), 7.50(m.3H), 7.80(d.1H), 7.90(m.1H), 8.04(m.1H).

5

e) Preparation of Compound(26)

Compound(26) was synthesised using compounds 12, 16 and 21 as intermediates in the same manner as the equivalent steps for synthesis of compound(27) (see Scheme 31).

10 Compound(26):

N.M.R. data (DMSO-d<sub>6</sub>)  $\delta$  1.70(m.1H), 2.40-4.15(m.14H), 5.20(m.2H), 7.20(2d.1H), 7.55(m.3H), 7.85(m.1H), 8.00(m.2H), 9.05-10.25(2br.d.2H).

Micro Analysis :	%Theory	C59.5, H6.99, N6.93.
(2HCl. 0.2H <sub>2</sub> O)	%Found	C59.3, H7.30, N6.70

15

Compound(16):

N.M.R. data (DMSO-d<sub>6</sub>, 373°K)  $\delta$  1.45(s.9H), 1.78(m.1H), 2.40-3.80(m.12H), 4.00(m.1H), 4.20(m.1H), 4.45(m.2H), 5.10(m.4H), 5.80(m.1H), 7.20(d.1H), 7.45(t.1H), 7.50(m.2H), 7.80(d.1H), 7.90(m.1H), 8.00(m.1H).

20

Compound(21):

N.M.R. data (DMSO-d<sub>6</sub>, 373°K)  $\delta$  1.30(m.1H), 1.48(s.9H), 2.30(m.1H), 2.56-3.70(m.14H), 5.15(m.2H), 7.30(d.1H), 7.47(t.1H), 7.53(m.2H), 7.83(d.1H), 7.94(m.1H), 8.05(m.1H).

25

f) Preparation of Compound(54)

A mixture of starting material (2S,4S)-2-[[N-(4-methoxybenzyl)-N-(naphthalen-1-ylmethyl)-amino]-methyl]-pyrrolidine-4-BOCthiol (compound(53))(100mg) and trifluoroacetic acid(5ml) was stirred at ambient temperature for 1 hour. The trifluoroacetic acid was removed under reduced pressure and the residue coevaporated with diethylether to give compound(54) as a colourless gum (83 mg).

30

SUBSTITUTE SHEET (RULE 26)

- 70 -

NMR data (CDCl<sub>3</sub>) δ 1.5(m, 1H), 1.75(br.d, 1H), 1.95(m, 1H), 2.6(t, 1H), 3.05(m, 1H), 3.2(d, 1H), 3.35(m, 2H), 3.85(s, 3H), 4.2(s, 2H), 4.6(2d, 2H), 6.95(d, 2H), 7.4(d, 2H), 7.6(m, 4H), 7.9(m, 3H).

5 Micro Analysis: %Theory C52.0, H5.40, N3.90  
(2.5TFA, 0.4 diethyl ether) %Found C52.0, H4.92, N3.96.

The starting material was prepared as follows.

A mixture of compound(12)(240 mg), dimethylformamide(20 ml), anhydrous potassium  
10 carbonate(80 mg) and *p*-methoxybenzylchloride(0.143ml) was stirred at 70° under an argon atmosphere for 4 hours. The solvent was removed under reduced pressure and the residue purified by column chromatography eluting with ethyl acetate/hexane(20:80) to give a colourless gum (2S,4S)-1-allyloxycarbonyl-2-[{*N*-(4-methoxybenzyl)-*N*-(naphthalen-1-ylmethyl)-amino}-methyl]-pyrrolidine-4-BOCthiol (compound(52)) (213 mg).

15 NMR data (CDCl<sub>3</sub>) δ 1.45(s, 9H), 2.15(m, 1H), 2.5(m, 1H), 2.8(m, 1H), 3.05(m, 1H), 3.5(m, 2H), 3.8(br.s, 7H), 3.9(m, 1H), 4.2(m, 1H), 4.6(s, 2H), 5.25(m, 2H), 5.9(m, 1H), 6.85(d, 2H), 7.2(d, 2H), 7.4(m, 4H), 7.8(2d, 2H), 8.1(d, 1H).

Tributyltin hydride(0.77ml) was added to a mixture of compound(52) and bis(triphenyl  
20 phosphine) palladium (O) chloride(2 mg) in dichloromethane(10 ml). The solution was stirred at ambient temperature for 30 minutes. A second portion of tributyltin hydride(0.335 ml) and bis(triphenylphosphine) palladium (O) chloride(2 mg) were added and the stirring was continued for a further 30 minutes. The mixture was applied directly to a silica flash column which was eluted with ethyl acetate/hexane(25:75),(50:50) and finally ethyl  
25 acetate. The product obtained was further purified by reverse phase HPLC on a C18 column eluting with water/methanol/TFA(20:80:0.2) to give the desired starting material (compound(53)) as a colourless gum, (168 mg.)

NMR data (CDCl<sub>3</sub>) δ 1.45(s, 9H), 1.55(m, 1H), 2.0(m, 1H), 2.5(m, 1H), 3.1(d, 1H),  
30 3.4(m, 3H), 3.6(t, 1H), 3.8(s, 3H), 4.1(2d, 2H), 4.4(d, 1H), 4.6(d, 1H), 6.95(d, 2H), m 7.4(d, 2H), 7.5(m, 4H), 7.9(m, 3H).

SUBSTITUTE SHEET (RULE 26)



- 71 -

Micro Analysis:                      %Theory C54.4. H5.40. N3.70  
(2TFA)                                  %Found C55.0. H5.31. N3.89

Example 25 (see Scheme 32)

5 **Preparation of**

a) **(2S,4S)-2[(N-methylnaphthalen-1-ylamino)-methyl]-4-sulfanylpyrrolidine**  
(compound 36) and:

b) **N-(naphthalen-1-yl)-N-((2S,4S)-4-sulfanylpyrrolidin-2-yl-methyl)-3-methylbutanamide** (compound 37).

10

Preparation of Compound 36

A mixture of starting material (2S,4S)-2[(N-methylnaphthalen-1-ylamino)-methyl]-4-BOCsulfanylpyrrolidine (compound (34)) (110 mg) and trifluoroacetic acid (5 ml) was stirred at ambient temperature for 1 hour. The trifluoroacetic acid was removed under  
15 reduced pressure and the residue dried under high vacuum to give compound(36) as a colourless gum(110 mg).

N.M.R. data (CDCl<sub>3</sub>) δ 1.7 (m,1H), 1.9 (d,1H), 2.6 (m,1H), 2.95 (s,3H), 3.1 (2d,1H), 3.5 (m,1H), 3.65 (m,3H), 4.05 (m,1H), 7.0 (br. s,1H), 7.4 (t,1H), 7.55 (m,3H), 7.7 (d,1H), 7.85  
20 (m,1H), 8.2 (m,1H).

Micro Analysis:                      %Found C 45.5. H 4.2. N 5.0  
(2.0TFA. 1.0H<sub>2</sub>O)                      %Theory C 46.3. H 4.67. N 5.4

25 The starting material for compound(36) was prepared as follows:

A mixture of (2S,4S)-2-formyl-4-BOCsulfanyl- pyrrolidine-1-carboxylic acid allyl ester (compound(1)) ( 711 mg), ethanol(25 ml), 1-naphthylamine(333 mg) and 3A molecular sieves(4.5 g.) was stirred under an argon atmosphere at ambient temperature for 6 hours.  
30 Acetic acid (0.4ml) was added followed by sodium cyanoborohydride(170 mg). The mixture was then stirred for a further 20 hours when the sieves were removed by

**SUBSTITUTE SHEET (RULE 26)**

- 72 -

filtration. The filtrate was concentrated under reduced pressure and the residue applied to a silica column and eluted with ethyl acetate/ hexane(20:80) to give (2S,4S)-1-allyloxycarbonyl-2[(naphthalen-1-ylamino)-methyl]-4-BOCsulfanylpyrrolidine (compound(31)) as a clear oil (560 mg).

5

N.M.R. data (CDCl<sub>3</sub>)  $\delta$  1.5 (s,9H), 1.85 (m,1H), 2.7 (m,1H), 3.35 (m,2H), 3.5 (m,1H), 3.8 (m,1H), 4.2 (m,1H), 4.5 (m,1H), 4.65 (d,2H), 5.3 (2d,2H), 5.95 (m,1H), 6.55 (m,1H), 7.2 (d,1H), 7.3 (t,1H), 7.4 (m,2H), 7.75 (m,1H), 7.9 (m,1H).

- 10 A mixture of (compound(31))(218 mg), dimethylformamide(40ml), iodomethane(0.6 ml.) and anhydrous potassium carbonate(150 mg) was stirred at 80° for 20 hours. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate(30 ml.) and washed with water(20ml). The organic phase was dried over magnesium sulphate, filtered and concentrated under reduced pressure to give (2S,4S)-1-allyloxycarbonyl-2[(N-
- 15 methyl-naphthalen-1-ylamino)-methyl]-4-BOCsulfanylpyrrolidine (compound(32)) as a yellow gum (183 mg).

- N.M.R. data (CDCl<sub>3</sub>)  $\delta$  1.45 (s,9H), 2.0 (m,1H), 2.4 (m,1H), 2.85 (s,3H), 3.0 (2d,1H), 3.25 (m,1H), 3.7 (2d,1H), 3.8 (m,1H), 4.1 (m,2H), 4.6 (d,2H), 5.3 (9m,2h), 5.95 (m,1H),
- 20 7.45 (m,5H), 7.8 (m,1H), 8.25 (m,1H).

- To a solution of compound(32)(178 mg) in dichloromethane(10 ml) was added tri-n-butyl tin hydride(0.2 ml.) followed by bis(triphenyl phosphine) palladium chloride (2 mg) and the mixture then stirred at ambient temperature. After 10min and 20min a second and
- 25 third portion of tri-n-butyl tin hydride (0.2ml.) and bis(triphenyl phosphine) palladium chloride (2 mg) were added and stirring continued for a further 90 min. The reaction solution was applied direct to a silica column and eluted with ethyl acetate/hexane(25:75), (50:50) and ethyl acetate. The product was further purified on a reverse phase HPLC, C18 column which was eluted with water/methanol/ trifluoroacetic acid(20:80:0.2) to give as a
- 30 colourless gum the desired starting material (compound(34))(160 mg).

- 73 -

N.M.R. data ( $\text{CDCl}_3$ )  $\delta$  1.45 (s,9H), 2.2 (s,1H), 2.39 (m,1H), 2.85 (s,3H), 2.9 (2d,1H), 3.1 (2d,1H), 3.25 (m,2H), 3.4 (m,1H), 3.6 (m,1H), 7.15 (d,1H), 7.45 (m,4H), 7.8 (m,1H), 8.35 (m,1H).

5 Micro Analysis: %Found C 50.8, H 5.20, N 4.6  
(2.0TFA, 0.5H<sub>2</sub>O) %Theory C 49.3, H 5.13, N 4.6

b) Preparation of Compound (37)

10 A mixture of starting material (compound(35))(187 mg) and trifluoroacetic acid(5 ml.) was stirred at ambient temperature for 1 hour. The trifluoroacetic acid was removed under reduced pressure and the residue dried under high vacuum to give a colourless gum, compound (37)(200 mg.).

15 N.M.R. data ( $\text{CDCl}_3$ )  $\delta$  0.8 (m,6H), 1.6-2.2 (m,5H), 2.6 (m,1H), 3.2-5.0 (m,6H), 7.6 (m,5H), 8.0 (m,2H).

Micro Analysis: %Found C 48.4, H 4.80, N 4.5  
(2.0 TFA, 1.0H<sub>2</sub>O) %Theory C 49.0, H 5.14, N 4.76

20

The starting material was prepared as follows.

Isovaleryl chloride(0.164 ml.) was added dropwise over 10 minutes to a stirred solution of compound(31)(297 mg.), dichloromethane(50 ml) and triethylamine(0.136 ml.). The solution was stirred at ambient temperature for 24 hours. The solvent was removed under  
25 reduced pressure and the residue applied directly to a silica column and eluted with ethyl acetate/hexane(25/75) to give a white foam, N-(naphthalen-1-yl)-N-((2S,4S)-1-allyloxycarbonyl-4-BOCsulfanylpyrrolidin-2-yl-methyl)-3-methylbutanamide, (compound(33))(329 mg).

N.M.R. data ( $\text{CDCl}_3$ )  $\delta$  0.75 (m,6H), 1.5 (s,9H), 1.65 -2.7 (m,5H), 3.15 -6.0 (m,9H),  
30 7.25 (m,1H), 7.5 (m,3H), 7.7 (m,1H), 7.9 (m,2H).

- 74 -

- To a solution of compound(33)(296 mg.) in dichloromethane(10 ml) was added tri-n-butyl tin hydride (0.3 ml.) followed by bis(triphenyl phosphine) palladium chloride(2 mg.). The solution was stirred at ambient temperature. After 10min and 20min a second and third portion of tri-n-butyl tin hydride(0.3 ml.) and bis(triphenyl phosphine) palladium chloride(2 mg) were added and the stirring continued for a further 30 minutes. The reaction solution was applied directly to a silica column which was then eluted with ethyl acetate/hexane(25:75), (50:50) and ethyl acetate. The product was further purified on a reverse phase HPLC . C18 column eluting with water/methanol/trifluoroacetic acid(20:80:0.2) to give the desired starting material, (compound (35))(216 mg.).
- 10 N.M.R. data ( $\text{CDCl}_3$ )  $\delta$  0.8 (m,6H), 1.49(s,9H), 1.1 -2.2 (m,6H), 2.9 -5.6 (m,6H), 7.4 - 8.0 (m,7H).

Micro Analysis:	%Found	C 57.0, H 6.20, N 4.80
(1.0TFA, 0.75H <sub>2</sub> O)	%Theory	C 56.9, H 6.45; N 4.91

15 Example 26 (see Scheme 33)

**Preparation of**

- a) **3-Methyl-N-(3,3-diphenylpropyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-butanamide** (compound 43) and;
- b) **N-(3,3-diphenylpropyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-butanamide** (compound 44)
- 20

Compounds (43) and (44) were synthesised using the procedure described in Example 23 using appropriate starting materials and intermediates as set out in Scheme 33.

25 a) Preparation of Compound (43)

Compound (43) :

NMR data (DMSO-d<sub>6</sub> at 373 ° K.)  $\delta$  0.9(d, 6H), 1.7(m, 1H), 2.1(m, 1H), 2.33(m, 2H), 2.45(m, 1H), 2.9-4.00(m, 9H), 4.2-4.95(m, 2H), 7.3-8.1(m, 10H), 9.65(v.br.s, 2H)

Micro Analysis:	%Theory	C64.8, H7.7, N5.9
1.00HCl. 1H <sub>2</sub> O	%Found	C64.5, H7.9, N6.0

30

- 75 -

The starting material 3-Methyl-N-(3,3-diphenylpropyl)-N-([2S,4S]-4-BOCsulfanylpyrrolidin-2-ylmethyl)-butanamide (compound 41) was synthesised from compound (1) and 3,3-diphenylpropylamine using a similar procedure to that outlined in Example 23.

5

Compound (38) :

NMR data (CDCl<sub>3</sub>) d 1.5(s, 9H), 1.8(m, 1H), 2.19(m, 2H), 2.42(m, 1H), 2.55(m, 2H), 2.7(m, 1H), 2.82(m, 1H), 3.19(m, 1H), 3.67(m, 1H), 4.0(m, 3H), 4.55(d, 2H), 5.2(2d, 2H), 5.9(m, 1H), 7.2(m, 10H).

10

Compound (39) :

NMR data (CDCl<sub>3</sub>) d 0.75-1.0(m, 6H), 1.22(m, 1H), 1.5(s, 9H), 1.78-2.02(m, 2H), 2.3(m, 4H), 3.2(m, 3H), 3.4-4.2(m, 6H), 4.52(m, 2H), 5.21(m, 2H), 5.9(m, 1H), 7.2(m, 10H) .

15 Compound (41) :

NMR data (CDCl<sub>3</sub>) d 0.75-1.00(m, 6H), 1.25(m, 1H), 1.5(s, 9H), 1.85-2.4(m, 6H), 2.83(m, 1H), 3.05-3.47(m, 6H), 3.6(m, 1H), 3.87(2t, 1H), 7.25(m, 10H) .

b) Preparation of Compound (44)

20 Characterisation data is set out below:

Compound (44):

NMR data (DMSOd<sub>6</sub> at 373° K) d 1.65(m, 1H), 1.85(s, 3H), 2.32(q, 2H), 2.45(m, 1H), 2.69-4.3(m, 9H), 7.2(m, 10H), 9.37(v.br.s, 2H).

Micro Analysis: %Theory C 63.3, H 7.3, N, 6.6

25 1.00 HCl, 0.75H<sub>2</sub>O %Found C63.1, H 7.3, N, 6.7

Compound (40):

NMR data (CDCl<sub>3</sub>) d 1.5(s, 9H), 1.82(s, 3H), 1.6-2.5(m, 4H), 3.2(m, 3H), 3.32-4.25(m, 6H), 4.54(m, 2H), 5.23(m, 2H), 5.9(m, 1H), 7.23(m, 10H).

30

- 76 -

Compound (42):

NMR data (CDCl<sub>3</sub>) δ 1.48(s, 9H), 1.8(m, 1H), 1.87(s, 2H), 2.07(s, 1H), 2.33(m, 3H), 2.83(m, 1H), 3.28(m, 6H), 3.6(m, 1H), 3.85(m, 1H), 7.25(m, 10H).

5 Example 27 (see Scheme 34)

**Preparation of**

a) **3-Methyl-N-(naphthalen-2-ylmethyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-butanamide** (compound 50) and;

b) **N-(naphthalen-2-ylmethyl)-N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-**

10 **acetamide** (compound 51)

Compounds (50) and (51) were synthesised using the procedure described in Example 23 using appropriate starting materials and intermediates as set out in Scheme 34.

15 a) Preparation of Compound (50).

Compound 50:

NMR data (DMSOd<sub>6</sub>) δ 0.75-1.1(m, 6H), 1.63(m, 1H), 2.1(m, 1H), 2.48(m, 1H), 2.83(m, 3H), 3.0-4.95(m, 8H), 7.17(m, 7H).

Micro Analysis: %Theory C64.2, H7.44, N7.13.

20 (1.0 HCl) %Found C64.0, H7.40, N7.10.

Starting material 3-Methyl-N-(naphthalen-2-ylmethyl)-N-([2S,4S]-4-

BOCsulfanylpyrrolidin-2-ylmethyl)-butanamide (compound (48)) was synthesised from compound (1) and 2-naphthylmethylamine.

25

Compound (45):

NMR data (CDCl<sub>3</sub>) δ 1.48(s, 9H), 1.92(m, 1H), 2.5(m, 1H), 2.82(m, 1H), 2.96(m, 1H), 3.2(2d, 1H), 3.7(m, 1H), 3.96(s, 2H), 4.08(m, 2H), 4.54(m, 2H), 5.2(m, 2H), 5.9(m, 1H), 7.42(m, 3h), 7.8(m, 4H).

30

- 77 -

Compound (46):

NMR data (CDCl<sub>3</sub>) δ 0.96(2d, 6H), 1.48(s, 9H), 1.9(m, 1H), 2.13-2.6(m, 4H), 3.3(m, 1H), 3.72(m, 2H), 4.15(m, 2H), 4.5(m, 2H), 4.76(m, 1H), 5.2(m, 2H), 5.9(m, 1H), 7.48(m, 3H), 7.73(m, 4H).

5

Compound (48):

NMR data (CDCl<sub>3</sub>) δ 0.98(2d, 6H), 1.3(m, 1H), 1.48(s, 9H), 2.3(m, 4H), 2.9(m, 1H), 3.1-3.7(m, 5H), 4.85(m, 2H), 7.15-7.9(m, 7H).

10 b) Preparation of Compound (51)

Characterisation data is set out below.

Compound 51:

NMR data (DMSO-d<sub>6</sub> at 373 °K) δ 1.7(m, 1H), 2.14(s, 3H), 2.47(m, 1H), 2.8-4.00(m, 6H), 4.8(m, 2H), 7.32-8.1(m, 7H).

15

Micro Analysis: %Theory C64.2, H7.44, N7.13.

(1.00 HCl) %Found C64.0, H7.40, N7.10.

Compound (47):

20 NMR data (CDCl<sub>3</sub>) δ 1.5(s, 9H), 1.9(m, 1H), 2.12(s, 2H), 2.29(s, 1H), 2.5(m, 1H), 3.18-5(m, 10H), 5.2(m, 2H), 5.95(m, 1H), 7.2-7.89(m, 7H).

Compound (49):

NMR data (CDCl<sub>3</sub>) δ 1.3(m, 1H), 1.47(s, 9H), 2.15(s, 2H), 2.3(s, 1H), 2.35(m, 1H), 2.88(m, 1H), 3.1-3.7(m, 5H), 4.85(m, 2H), 7.4-7.9(m, 7H).

25

Example 28 (see scheme 35)

**(2S)-2-({4-([([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-amino]-naphthalene-2-carbonyl)-amino}-4-methylsulfanylbutyric acid methyl ester (compound 30)**

30 Starting material (2S)-2-({4-([([2S,4S]-4-BOCsulfanylpyrrolidin-2-ylmethyl)-amino]-naphthalene-2-carbonyl)-amino}-4-methylsulfanylbutyric acid methyl ester **30e**

SUBSTITUTE SHEET (RULE 26)

- 78 -

(72.1mg, 0.132mmol) was deprotected (analogously as for the equivalent step in **Example 15**) to give the title compound **30**. 76mg (97.8%).

$^1\text{H}$  NMR ( $\text{CDCl}_3 + \text{CD}_3\text{COOD}$ , 200MHz)  $\delta$  1.75-2.0 (1H, m); 2.0-2.5 (5H + DMSO, m);

2.55-3.0 (3H, m); 3.15-3.4 (1H, m); 3.5-3.7 (1H, m); 3.7-3.9 (6H, m); 4.2-4.4 (1H, m);

5 4.9-5.05 (1H, m); 7.0-8.1 (6H, m, ArH).

MS ( $\text{ESP}^+$ )  $m/z$  448 ( $\text{M} + \text{H}$ ) $^+$ .

Anal. Calcd for  $\text{C}_{22}\text{H}_{29}\text{N}_3\text{S}_2\text{O}_3 \cdot 1.25\text{ TFA}$  C, 49.9; H, 5.17; N, 7.12

Found

C, 49.6; H, 5.3; N, 6.7

10 Starting material **30e** was prepared as follows.

Compound 30a

2-Naphthoic acid was nitrated with conc  $\text{HNO}_3$  (Tetrahedron **49**, 17, 3655, 1993) to give a mixture of nitro-acids **30a**, containing the required 4-Nitro-2-Naphthoic acid.

MS ( $\text{ESP}^+$ )  $m/z$  216 ( $\text{M} - \text{H}$ ) $^-$ .

15

Compound 30b

Oxalyl chloride (6.0mL, 68.7mmol) was added dropwise to a stirred solution of the nitro acid mixture, **30a** (7.3g, 33.6mmol) in a mixture of DMF (1.0mL) and  $\text{CH}_2\text{Cl}_2$  (100mL) at  $0^\circ\text{C}$  under argon. The solution was allowed to warm to RT, stirred 18hrs, evaporated to

20 dryness and azeotroped with toluene (2x25mL). The resulting residues were redissolved in  $\text{CH}_2\text{Cl}_2$  (100mL) and cooled to  $0^\circ\text{C}$  under argon.

$\text{Et}_3\text{N}$  (7.0mL, 50mmol) was then added, followed by L-Methionine methylester hydrochloride (7.4g, 37mmol), portionwise, such that the internal temperature did not rise above  $10^\circ\text{C}$ . The reaction mixture was left to warm to room temperature and stirred for 18hr

25 washed with water (100mL), dried over  $\text{MgSO}_4$ , filtered and concentrated to a viscous brown gum. This was then purified by flash chromatography on  $\text{SiO}_2$  (Merck 9385), eluting with 25% EtOAc/i-Hexane. Appropriate fractions were combined and evaporated to give **30b** as a viscous orange gum, 490mg (4%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200MHz)  $\delta$  2.1-2.5 (5H, m); 2.55-2.75 (2H, m); 3.85 (3H, s);

30 4.9-5.1 (1H, m); 7.32 (1H, d); 7.6-8.0 (2H, m); 8.05 (1H, dd); 8.5-8.7 (3H, m).

MS ( $\text{ESP}^+$ )  $m/z$  363 ( $\text{M} + \text{H}$ ) $^+$ .

SUBSTITUTE SHEET (RULE 26)



- 79 -

Compound 30c

**30b** (450mg, 1.24mmol) was reduced (analogously as for the equivalent step in **Example 22**) to give the corresponding aniline **30c** as a yellow gum. 310mg (75.3%)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 250MHz) δ 2.0-2.45(5H, m); 2.5-2.75(2H, m); 3.83(3H, s);

5 4.3(2H, bs, NH<sub>2</sub>); 4.9-5.05(1H, m); 7.0(1H, d, NHCO); 7.2(1H, d); 7.45-7.65(2H, m); 7.72(1H, s); 7.8-8.0(2H, m).

MS (ESP<sup>+</sup>) m/z 333 (M+H)<sup>+</sup>, 271, 170.

Compound 30d

10 **30c** (300mg, 0.9mmol) was coupled with the aldehyde **22b** (428mg, 1.36mmol) under the conditions employed to synthesise **22g** using MeOH as solvent and in the presence of 3 Å<sup>0</sup> molecular sieves as drying agent to give **30d** as yellow gum. 460mg (76.5%)

MS (ESP<sup>+</sup>) m/z 632 (M+H)<sup>+</sup>

15 Compound 30e

**30d** (450mg, 0.7mmol) was deprotected (analogously as for the equivalent step in **Example 15**) to give the desired starting material **30e**. 220mg (56.4%)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200MHz) δ 1.4-1.9(10H+H<sub>2</sub>O, m); 2.0-2.75(9H, m); 2.95(1H, q);

3.1-3.35(1H, m); 3.35-3.55(2H, m); 3.55-3.8(2H, m); 3.82(3H, s, CO<sub>2</sub>Me); 4.98(1H, m);

20 5.15(1H, bs, NH); 6.9-7.1(2H, m, ArH+NHCO); 7.4-7.6(2H, m); 7.61(1H, d); 7.8-8.0(2H, m).

MS (ESP<sup>+</sup>) m/z 548 (M+H)<sup>+</sup>, 448.

Example 29 (see scheme 36)

## 25 Preparation of

a) (2S)-2-({3-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-naphthalene-1-carbonyl)-amino-4-methylsulfanylbutyric acid methyl ester (compound 31)

b) (2S)-2-({3-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-naphthalene-1-carbonyl)-amino-4-methylsulfanylbutyric acid (compound 31f)

30

- 80 -

a) Preparation of Compound 31

**31e** (55mg, 0.1mmol) was deprotected (analogously as for the equivalent step in **Example 15**) then treated with  $\text{Et}_2\text{O} \cdot \text{HCl}$  to give the title compound **31** as a white solid.

(37mg, 64.8%)

5  $^1\text{H}$  NMR ( $\text{DMSO}-d_6 + \text{CD}_3\text{CO}_2\text{D}$ , 250MHz)  $\delta$  1.05 (1H, t,  $(\text{CH}_3\text{CH}_2)_2\text{O}$ ); 1.6-1.8 (1H, m); 1.9-2.15 (4H, m); 2.3-2.7 (4H + DMSO, m); 3.0-4.0 (9H +  $(\text{CH}_3\text{CH}_2)_2\text{O}$ ); 4.55-4.7 (1H, m); 6.95 (1H, s); 7.1 (1H, s); 7.15 (1H, t); 7.32 (1H, t); 7.62 (1H, d); 7.92 (1H, d)

MS ( $\text{ESP}^+$ )  $m/z$  448 ( $\text{M} + \text{H}$ ) $^+$ .

Anal. Calcd for  $\text{C}_{22}\text{H}_{29}\text{N}_3\text{S}_2\text{O}_3 \cdot 2.7\text{HCl} \cdot 0.3\text{Et}_2\text{O}$  C, 49.0; H, 6.15; N, 7.39

10 Found

C, 49.1; H, 6.1; N, 7.2

Compound 31a

3-Nitro-1-naphthoic acid **31a** was synthesised from 3-nitro-1,8-naphthalic anhydride according to the method of G.J. Leuck et al (Journal of the American Chemical Society

15 51, 1831, 1929).

Compound 31b

3-Nitro-1-Naphthoic acid **31a** (5.0g, 23.04mmol) was coupled with L-Methionine methylester hydrochloride (analogously as for the equivalent step in **Example 22**) to give

20 **31b** as a white crystalline solid. 2.53g (30.3%)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200MHz)  $\delta$  2.0-2.5 (5H, m); 2.55-2.75 (2H, m); 3.85 (3H, s); 5.05 (1H, m); 6.9 (1H, d, NH); 7.6-7.85 (2H, m); 8.0-8.15 (1H, m); 8.3-8.5 (2H, m); 8.83 (1H, m)

MS ( $\text{ESP}^+$ )  $m/z$  363 ( $\text{M} + \text{H}$ ) $^+$

25 Compound 31c

**31b** (2.3g, 6.35mmol) was reduced (analogously as for the equivalent step in **Example 22**) to give the corresponding aniline **31c** as a yellow gum. 1.75g (83%)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250MHz)  $\delta$  2.05-2.2 (4H, m); 2.25-2.45 (1H, m); 2.63 (2H, m); 3.83 (3H, s); 5.03 (1H, m); 6.66 (1H, d); 7.05 (1H, m); 7.15 (1H, m); 7.28 (1H, m); 7.39 (1H, m); 7.6 (1H, m); 8.15 (1H, m)

30

MS ( $\text{ESP}^+$ )  $m/z$  333 ( $\text{M} + \text{H}$ ) $^+$ , 170.

- 81 -

Compound 31d

**31c** (1.7g, 5.12mmol) was coupled with the aldehyde **22b** (1.76g, 5.59mmol). (analogously as for the equivalent step in **Example 30**) to give **31d** as an off-white foam. 2.95g (91.3%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>+CD<sub>3</sub>COOD, 250MHz) δ 1.5 (9H, s); 1.9 (1H, m);

5 2.0-2.25 (4H+CH<sub>3</sub>COOH, m); 2.25-2.44 (1H, m); 2.55-2.75 (3H, m); 3.25-3.53 (2H, m);

3.55-3.7 (1H, m); 3.7-3.95 (4H, m); 4.1-4.25 (1H, m); 4.25-4.4 (1H, m); 4.55-4.8 (2H, m);

5.03 (1H, m); 5.15-5.45 (2H, m); 5.96 (1H, m); 6.9-7.5 (4H+CHCl<sub>3</sub>, m); 7.66 (1H, m);

8.1 (1H, m)

MS (ESP+) m/z 632 (M+H)<sup>+</sup>.

10

Compound 31e

**31d** (2.0g, 3.17mmol) was deprotected (analogously as for the equivalent step in **Example 15**) to give the desired starting material **31e** as a pale yellow foam. 1.62g (93.4%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ 2.4-2.6 (10H, m); 1.85 (4H, bs); 2.0-2.2 (4H, m);

15 2.35 (1H, m); 2.5 (1H, m); 2.65 (2H, t); 2.9 (1H, m); 3.1 (1H, m); 3.3 (1H, m); 3.4 (1H, m);

3.55 (1H, m); 3.65 (1H, m); 3.8 (3H, s); 5.02 (1H, m); 6.65 (1H, d); 6.9 (1H, m); 7.1 (1H, m);

7.2-7.3 (1H+CHCl<sub>3</sub>, m); 7.4 (1H, m); 7.62 (1H, m); 8.1 (1H, m)

MS (ESP+) m/z 548 (M+H)<sup>+</sup>. 448.

20 b) Compound 31f

**31e** (180mg, 0.33mmol) was hydrolysed (analogously as for **Example 16**) then purified by reverse phase HPLC (Dynamax® 60A, C<sub>18</sub>, 8m prep column), eluting with 50% MeOH/H<sub>2</sub>O (0.1% TFA) to give product **31f** as a white foam. 126mg (65.9%).

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>+CD<sub>3</sub>COOD, 300MHz) δ 1.5-1.8 (1H, m); 1.9-2.1 (5H, m);

25 2.4-2.7 (3H+DMSO, m); 3.0-3.1 (1H, m); 3.4-3.7 (4H, m); 3.75-3.9 (1H, m); 4.57 (1H, m);

6.9 (1H, m); 7.07 (1H, m); 7.17 (1H, m); 7.35 (1H, m); 7.63 (1H, m); 7.95 (1H, m)

MS (ESP+) m/z 434 (M+H)<sup>+</sup>. 285.

Anal. Calcd for C<sub>21</sub>H<sub>27</sub>N<sub>3</sub>S<sub>2</sub>O<sub>3</sub>·1.3TFA C, 48.7; H, 4.9; N, 7.22

Found C, 48.6; H, 4.9; N, 7.1

30

SUBSTITUTE SHEET (RULE 26)

- 82 -

Example 30 (see Scheme 37)

Preparation of

- a) (2S)-2-((-3-phenyl-5-([(2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester (compound 32)
- 5 and;
- b) (2S)-2-((-3-phenyl-5-([(2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid (compound 32f)

a) Preparation of Compound 32

- 10 Starting material compound 32e (55mg,0.096mmol) was deprotected (analogously as for the equivalent step in **Example 15**) to give the title compound **32** as a white foam (56mg).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>,250MHz) δ 1.6-1.85(1H.m);1.9-2.4(6H+CH<sub>3</sub>C<sub>5</sub>H<sub>6</sub>);2.45-2.7(3H.m);  
3.1-3.25(1H.m);3.35-4.1(11H+H<sub>2</sub>O.m);4.75-4.95(1H.m);6.8(1H.m);6.9-7.05(1H.m);  
7.1-7.55(6H+CH<sub>3</sub>C<sub>6</sub>H<sub>5</sub>+CHCl<sub>3</sub>.m.)

- 15 MS (ESP+) m/z 474 (M+H)<sup>+</sup>.

Anal.Calcd for C<sub>24</sub>H<sub>31</sub>N<sub>3</sub>O<sub>3</sub>S<sub>2</sub>.2TFA.0.75toluene C,51.8;H,5.1;N,5.45

Found C,51.6;H,5.2;N,5.1

Starting material 32e was prepared as follows.

20

Compound 32a

Saturated NaHCO<sub>3</sub>(aq) (90mL) was added to a stirred solution of methyl-3-bromo-5-nitrobenzoate (4.0g,15.38mmol) (Mindl and Vecera, Coll.Czech.Chem.Comm. **38**,3496.1973.) and phenyl boronic acid (2.0g,16.38mmol) in dimethoxyethane (180mL).

- 25 Tetrakis(triphenylphosphine)palladium(0), (444mg,0.38mmol) was added and the mixture heated at reflux for 1hr. The resulting black solution was allowed to cool to RT then quenched with saturated NaHCO<sub>3</sub>(aq)(400mL). The aqueous was extracted with EtOAc(200mL),then acidified to pH3 with 2N HCl. The resulting suspension was filtered,washed with water and azeotroped with toluene (3x25mL) to give **32a** as an off-
- 30 white solid which was triturated with i-Hexane.filtered and dried.2.6g(69.5%).

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>,300MHz) δ 7.5(3H.m);7.8(2H.m);8.4-8.7(3H.m)

SUBSTITUTE SHEET (RULE 26)

- 83 -

MS (ESP<sup>+</sup>) m/z 242 (M-H)<sup>+</sup>.Anal. Calcd for C<sub>13</sub>H<sub>9</sub>NO<sub>4</sub>: C.64.2:H.3.73:N.5.76

Found C.64.0:H.3.7:N.5.6

5 Compound 32b

**32a** (3.1g, 12.76mmol) was coupled with L-Methionine methylester hydrochloride (analogously as for the equivalent step in **Example 22**) to give **32b**. 4.9g (99%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 200MHz) δ 2.1-2.45 (5H, m); 2.65 (2H, t); 3.83 (3H, s); 4.99 (1H, m); 7.2-7.35 (1H + CHCl<sub>3</sub>, m); 7.4-7.6 (3H, m); 7.6-7.7 (2H, m); 8.38 (1H, m); 8.58 (2H, m)

10 MS (ESP<sup>+</sup>) m/z 389 (M+H)<sup>+</sup>.Anal. Calcd for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>S C.58.8:H.5.19:N.7.21

Found C.58.8:H.5.1:N.7.2

Compound 32c

15 **32b** (3.0g, 7.73mmol) was reduced (analogously as for the equivalent step in **Example 30**) to give the corresponding aniline **32c**. 2.43g (87.8%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 250MHz) δ 2.0-2.2 (4H, m); 2.2-2.4 (1H, m); 2.6 (2H, m); 3.8 (3H, s); 3.9 (2H, bs, NH<sub>2</sub>); 4.93 (1H, m); 6.93 (1H, d, NHCO); 7.03 (1H, m); 7.12 (1H, m); 7.3-7.5 (4H, m); 7.5-7.65 (2H, m)

20 MS (ESP<sup>+</sup>) m/z 359 (M+H)<sup>+</sup>.Compound 32d

**32c** (1.0g, 2.8mmol) was coupled with the aldehyde **22b** (880mg, 2.8mmol) (analogously as for the equivalent step in **Example 30**) to give **32d**. 1.51g (82.3%)

25 <sup>1</sup>H NMR (CDCl<sub>3</sub> + CD<sub>3</sub>COOD, 250MHz) δ 1.5 (9H, s); 1.8-2.0 (1H, m); 2.0-2.4 (5H + CH<sub>3</sub>COOH, m); 2.5-2.75 (3H, m); 3.2-3.45 (2H, m); 3.5-3.7 (1H, m); 3.7-3.9 (4H, m); 4.0-4.4 (2H, m); 4.5-4.75 (2H, m); 4.9-5.05 (1H, m); 5.1-5.45 (2H, m); 5.8-6.1 (1H, m); 7.03 (1H, m); 7.1-7.5 (5H + CHCl<sub>3</sub>, m); 7.55-7.7 (2H, m)

MS (ESP<sup>+</sup>) m/z 658 (M+H)<sup>+</sup>.30 Anal. Calcd for C<sub>33</sub>H<sub>43</sub>N<sub>3</sub>O<sub>7</sub>S<sub>2</sub>·0.1H<sub>2</sub>O C.59.9:H.6.61:N.6.35

Found C.59.7:H.6.8:N.6.2

SUBSTITUTE SHEET (RULE 26)

- 84 -

Compound 32e

**32d** (1.1g, 1.67mmol) was deprotected (analogously as for the equivalent step in **Example 15**) to give the desired starting material **32e**, 800mg (83.4%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 250MHz) δ 1.25 (1.5H, t, CH<sub>3</sub>CH<sub>2</sub>COCH<sub>3</sub>); 1.4-1.6 (10H, m);

5 1.9 (2H, bs, NH+H<sub>2</sub>O); 2.0-2.22 (4H+CH<sub>3</sub>CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>); 2.23-2.55 (2H, m);

2.51-2.65 (2H, m); 2.9 (1H, m); 3.12 (1H, m); 3.2-3.75 (4H, m); 3.8 (3H, m);

4.13 (1.3H, q, CH<sub>3</sub>CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>); 4.45 (1H, bs, NH); 4.95 (1H, m);

6.85-7.0 (2H, m, ArH+NHCO); 7.07 (1H, m); 7.2-7.5 (4H+CHCl<sub>3</sub>, m); 7.5-7.65 (2H, m)

MS (ESP+) m/z 574 (M+H)<sup>+</sup>, 474.

10 Anal. Calcd for C<sub>29</sub>H<sub>39</sub>N<sub>3</sub>O<sub>5</sub>S<sub>2</sub>·0.5EtOAc C, 60.3; H, 7.02; N, 6.8

Found

C, 59.9; H, 7.1; N, 6.6

b) Preparation of Compound 32f

15 Starting material **32e** (140mg, 0.244mmol) was hydrolysed (analogously as for the equivalent step in **Example 31**) to give the desired product **32f** as a white foam, 96.3mg (64.9%).

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>+CD<sub>3</sub>COOD, 250MHz) δ 1.5-1.8 (1H, m); 1.9-2.2 (5H, m);

3.05 (1H, q); 3.15-3.6 (7H, m); 3.65-3.9 (1H, m); 4.45-4.65 (1H, m); 6.95-7.05 (1H, m);

20 7.05-7.2 (1H, m); 7.25-7.5 (4H, m); 7.55-7.7 (2H, m).

MS (ESP+) m/z 460 (M+H)<sup>+</sup>, 279.

Anal. Calcd for C<sub>23</sub>H<sub>29</sub>N<sub>3</sub>S<sub>2</sub>O<sub>3</sub>·1.3TFA C, 50.6; H, 5.02; N, 6.91

Found

C, 50.6; H, 5.1; N, 7.2

25 The starting material was prepared as described in a) immediately above.

Example 31 (see Scheme 38)

Preparation of

a) (2S)-2-({2-phenyl-5-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-

30 phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester (compound 33)

and:

SUBSTITUTE SHEET (RULE 26)

- 85 -

b) (2S)-2-((2-phenyl-5-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino)-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid (compound 33f)

a) Preparation of Compound 33

- 5 Starting material **33e** (53.4mg,0.093mmol) was deprotected (analogously as for the equivalent step in **Example 31**) to give the title compound **33** as a white solid.43.2mg(87%).

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>+CD<sub>3</sub>COOD,300MHz) δ1.5-1.9(3H+CH<sub>3</sub>COOH.m);1.95(3H,s);  
2.0-2.3(2H.m);2.4-2.65(1H+DMSO.m);3.0-3.15(1H.m);3.3-3.9(8H.m);

- 10 4.25-4.4(1H,m);6.7(1H,m);6.78(1H,m);7.1-7.4(6H.m).

MS (CI<sup>+</sup>) m/z 474 (M+H)<sup>+</sup>.

Anal.Calcd for C<sub>24</sub>H<sub>31</sub>N<sub>3</sub>S<sub>2</sub>O<sub>3</sub>·1.75TFA C.53.6:H.6.14:N.7.82

Found C.53.6:H.6.3:N.7.7

- 15 The starting material was prepared as follows.

Compound 33a

2-Bromo-5-nitrobenzoic acid (12.28g,0.05mmol) was coupled with benzene boronic acid (6.7g,0.055mmol),(analogously as for the equivalent step in **Example32**) to give **33a** as a white solid.10.95g(90.3%).

- 20 <sup>1</sup>H NMR (DMSO-D<sub>6</sub>,300MHz) δ7.3-7.5(5H.m);7.65(1H.m);8.35(1H.m);8.45(1H.m).  
MS (ESP-) m/z 242 (M-H)<sup>-</sup>.198. .

Compound 33b

**33a** (3.58g,14.7mmol)was coupled with L-Methionine methyl ester hydrochloride

- 25 (3.25,16.2mmol),(analogously as for the equivalent step in **Example32**) to give **33b** as a pale yellow solid.3.02g(52.6%)

<sup>1</sup>H NMR (CDCl<sub>3</sub>,300MHz) δ1.7-2.2(7H.m);3.7(3H,s);4.7(1H.m);6.05(1H,m,NH);  
7.35-7.6(6H.m)8.33(1H.m);8.55(1H.m)

MS (ESP+) m/z 389 (M+H)<sup>+</sup>.

30

- 86 -

Compound 33c

**33b** (1.0g, 2.6mmol) was reduced (analogously as for the equivalent step in **Example 30**) to give the corresponding aniline **33c**. 725mg (78.6%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ 1.6-1.8 (1H, m); 1.8-2.15 (6H, m); 3.6 (3H, s);

5 3.7-3.9 (2H, bs, NH<sub>2</sub>); 4.6-4.7 (1H, m); 5.85 (1H, d, NHCO); 6.79 (1H, m); 7.0 (1H, m);  
7.15 (1H, d); 7.2-7.45 (5H + CHCl<sub>3</sub>, m).

MS (ESP+) m/z 359, (M+H)<sup>+</sup>, 196.

Compound 33d

10 **33c** (710mg, 1.98mmol) was coupled with the aldehyde **22b** (625mg, 1.98mmol) (analogously as for the equivalent step in **Example 30**) to give **33d**. 1.1g (84.4%).

<sup>1</sup>H NMR (CDCl<sub>3</sub> + CD<sub>3</sub>COOD, 250MHz) δ 1.5 (9H, s); 1.6-2.2 (8H + CH<sub>3</sub>COOH, m);

2.5-2.75 (1H, m); 3.2-3.4 (2H, m); 3.45-3.9 (5H, m); 4.05-4.35 (2H, m); 4.5-4.8 (3H, m);

5.15-5.45 (2H, m); 5.8-6.1 (1H, m); 6.75-6.9 (1H, m); 6.9-7.05 (1H, m); 7.1-7.23 (1H, m);

15 7.25-7.45 (5H + CHCl<sub>3</sub>, m).

MS (ESP+) m/z 658 (M+H)<sup>+</sup>.

Anal. Calcd for C<sub>33</sub>H<sub>43</sub>N<sub>3</sub>S<sub>2</sub>O<sub>7</sub> C, 60.3; H, 6.59; N, 6.39

Found

C, 60.0; H, 6.9; N, 6.2

20 Compound 33e

**33d** (1.0g, 1.52mmol) was deprotected (analogously as for the equivalent step in **example 15**) to give the desired starting material **33e**. 658mg (75.4%).

<sup>1</sup>H NMR (CDCl<sub>3</sub> + CD<sub>3</sub>COOD, 250MHz) δ 1.5 (9H, s); 1.6-2.2 (8H + CH<sub>3</sub>COOH, m);

2.55-2.75 (1H, m); 3.25-3.4 (1H, m); 3.5-3.75 (5H, m); 3.75-4.2 (3H, m);

25 4.55-4.75 (1H, m); 6.7-6.85 (1H, m); 6.85-6.97 (1H, m); 7.1-7.25 (1H, m);

7.25-7.48 (5H + CHCl<sub>3</sub>, m).

MS (ESP+) m/z 574 (M+H)<sup>+</sup>, 474.

Anal. Calcd for C<sub>29</sub>H<sub>39</sub>N<sub>3</sub>O<sub>5</sub>S<sub>2</sub> C, 60.7; H, 6.85; N, 7.32

Found

C, 60.7; H, 7.20; N, 7.30

30



- 87 -

b) Preparation of Compound 33f

Starting material **33e** (100mg, 0.174mmol) was hydrolysed (analogously as for the equivalent step in **Example 31**) to give **33f** as a white foam, 64.6mg (59.8%).

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>+CD<sub>3</sub>COOD, 300MHz) δ 1.5-2.0 (6H+CH<sub>3</sub>COOH, m);

5 2.0-2.3 (2H, m); 2.3-2.7 (1H+DMSO); 3.0-3.1 (1H, m); 3.2-3.9 (5H, m); 4.2-4.35 (1H, m);  
6.6-6.9 (2H, m); 7.1-7.4 (6H, m).

MS (ESP+) m/z 460 (M+H)<sup>+</sup>. 311.

Anal Calcd for C<sub>23</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>S<sub>2</sub> 1.4TFA C, 50.0; H, 4.95; N, 6.79

Found C, 49.9; H, 5.1; N, 6.7

10

Starting material **33e** was prepared as described in a) immediately above.

Example 32 (see Scheme 39)

Preparation of

15 a) **(2S)-2-{2-Benzyl-5-[(4-sulfanylpyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester** (compound 34) and:

b) **(2S)-2-{2-Benzyl-5-[(4-sulfanylpyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanylbutyric acid** (compound 34h)

20 a) Preparation of Compound 34

Starting material **34g** (500mg, 0.85mmol) was deprotected (analogously as for the equivalent step in **Example 31**) to give the title compound **34** as a white solid, 454mg (89.3%).

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>+CD<sub>3</sub>COOD, 300MHz) δ 1.5-1.7 (1H, m); 1.85-2.1 (5H, m);

25 2.35-2.6 (3H+DMSO, m); 2.9-3.1 (1H, m); 3.1-3.8 (8H, m); 3.9 (2H, q); 4.4-4.6 (1H, m);  
6.5-6.7 (>1H, m); 6.9-7.0 (1H, m); 7.0-7.3 (6H, m).

MS (ESP+) m/z 488 (M+H)<sup>+</sup>. 325.

Anal. Calcd for C<sub>25</sub>H<sub>33</sub>N<sub>3</sub>S<sub>2</sub>O<sub>3</sub>·3HCl C, 50.3; H, 6.08; N, 7.04

Found C, 50.4; H, 6.3; N, 7.3

30 Starting material **34g** was prepared as follows.

- 88 -

Compound 34a

A solution of 2-bromo-5-nitrobenzoic acid (9.0g, 36.6mmol) in MeOH (200mL) was treated with  $\text{SO}_2\text{Cl}_2$  (2.0mL) and the resulting solution heated at reflux for 18hrs. The reaction mixture was then evaporated, pre-absorbed on  $\text{SiO}_2$  (Merck.9385) and

5 chromatographed, eluting with 10%EtOAc/i-Hexane. Appropriate fractions were combined and evaporated to give **34a** as a crystalline white solid. 8.38g (88.1%)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$  4.0 (3H, s,  $\text{CO}_2\text{CH}_3$ ); 7.85 (1H, m); 8.18 (1H, m); 8.63 (1H, m).

Compound 34b

10 A solution of benzyl bromide (2.0mL, 17.3mmol) in THF (10mL) was added dropwise at  $0^\circ\text{C}$  to a stirred suspension of zinc dust (1.7g, 26mmol) in THF (10mL) which had been activated according to the method described by Knochel (J.O.C. 53, 2392, 1988). The mixture was left to warm to RT and stir for 3hrs. An aliquot (6.5mmol) of the supernatant containing the benzyl zinc reagent was then added to a stirred solution of **34a**

15 (1.0g, 3.85mmol) and  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (27mg, 0.0385mmol) in THF (10mL) at RT under argon. After 1hr a second aliquot (6.5mmol) of the benzyl zinc reagent was added. The resulting black reaction mixture was quenched with 2N HCl (250mL) and extracted with EtOAc (2x100mL). The combined organics were washed with water (50mL) and brine (50mL), filtered through phase separating paper and evaporated to an orange gum. This  
20 was chromatographed on  $\text{SiO}_2$  (Merck.9385) eluting with 10%EtOAc/i-Hexane to give **34b** as a yellow oil, 590mg (56.6%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$  3.9 (3H, s,  $\text{CO}_2\text{CH}_3$ ); 4.48 (2H, s,  $\text{CH}_2\text{Ph}$ ); 7.0-7.5 (6H, m); 8.23 (1H, m); 8.75 (1H, m).

MS (ESP $^+$ )  $m/z$  270 (M-H) $^+$ , 210.

25

Compound 34c

2N NaOH (2.0mL, 4mmol) was added to a solution of **34b** (560mg, 2.06mmol) in MeOH (10mL) at RT. After 2hrs the RM was evaporated to remove the MeOH and then partitioned between  $\text{Et}_2\text{O}$  (20mL) and 2N NaOH (20mL). The aqueous was acidified to pH 2/3 with 2N

30 HCl and extracted with EtOAc (3x20mL). The combined organics were washed with water

- 89 -

(20mL) and brine (20mL), filtered through phase separating paper and evaporated to yield **34c** as a white solid. 453mg (85.3%).

$^1\text{H}$  NMR (DMSO- $\text{D}_6$ , 300MHz)  $\delta$  4.45(2H, s,  $\text{CH}_2\text{Ph}$ ); 7.0-7.4(5H, m);

7.55(1H, m); 8.3(1H, m); 8.53(1H, m).

5 MS (ESP $^+$ )  $m/z$  256 (M-H) $^+$ . 212.

#### Compound 34d

**34c** (630mg, 2.45mmol) was coupled with L-Methionine methyl ester hydrochloride (540mg, 2.7mmol). (analogously as for the equivalent step in **Example 32**) to give **34d** as a  
10 pale yellow solid. 900mg (91.3%).

$^1\text{H}$  NMR (DMSO- $\text{D}_6$ , 250MHz)  $\delta$  1.9-2.25(5H, m); 2.5-2.75(2H + DMSO, m);

3.74(3H, s,  $\text{CO}_2\text{CH}_3$ ); 4.28(2H, q,  $\text{CH}_2\text{Ph}$ ); 4.55-4.75(1H, m); 7.15-7.5(5H, m);

7.6(1H, m); 8.2-8.35(2H, m); 9.13(1H, d,  $\text{NHCO}$ ).

MS (ESP $^+$ )  $m/z$  403 (M+H) $^+$ .

15

#### Compound 34e

$\text{SnCl}_4 \cdot 2\text{H}_2\text{O}$  (2.5g, 11.08mmol) was added to a stirred solution of **34d** (900mg, 2.24mmol) in EtOAc (50mL) and the resulting mixture heated at reflux for 18hrs. The RM was cooled to RT and treated with 0.8850 SG  $\text{NH}_3$ (aq) dropwise to pH8. The resulting heavy white  
20 precipitate was removed by filtration through celite(545). The filtrates were then evaporated and purified by chromatography (Mega Bond Elut,  $\text{SiO}_2$ ), eluting with  $\text{CH}_2\text{Cl}_2$  and then 50%EtOAc/ i-Hexane to give the corresponding aniline **34e**, 595mg (71.4%).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$  1.75-2.2(5H, m); 2.25-2.45(2H, m);

3.6-3.8(5H, m,  $\text{CO}_2\text{CH}_3 + \text{NH}_2$ ); 4.08(2H, q,  $\text{CH}_2\text{Ph}$ );

25 4.65-4.85(1H, m); 6.24(1H, d,  $\text{NHCO}$ ); 6.7(1H, m); 6.78(1H, m); 7.0(1H, m);

7.05-7.3(5H +  $\text{CHCl}_3$ , m).

MS (ESP $^+$ )  $m/z$  373 (M+H) $^+$ . 210.

30

- 90 -

Compound 34f

**34e** (570mg, 1.53mmol) was coupled with the aldehyde **22b** (580mg, 1.84mmol) (analogously as for the equivalent step in **Example 30**) to give **34f** as a crude pale green foam (1.54g).

5 MS (ESP+) m/z 672 (M+H)<sup>+</sup>.

Compound 34g

**34f** (1.5g, 2.24mmol) was deprotected (analogously as for the equivalent step in **Example 15**) to give the desired starting material **34g** as a pale brown glass. 550mg

10 (41.9%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ 1.3-1.65 (10H, m); 1.7-2.2 (5H + H<sub>2</sub>O, m); 2.25-2.6 (3H, m); 2.8-3.9 (9H, m); 3.9-4.25 (2H, m); 4.6-4.9 (1H, m); 6.3 (1H, d, NHCO); 6.55-6.8 (2H, m); 6.9-7.4 (5H + CHCl<sub>3</sub>, m).

MS (ESP+) m/z 588 (M+H)<sup>+</sup>, 488.

15

b) Preparation of Compound 34h

Starting material **34g** (52mg, 0.087mmol) was hydrolysed (analogously as for the equivalent step in **Example 16**), then purified by reverse phase HPLC (Dynamax® 60A, C<sub>18</sub>, 8m prep column), eluting with 50% MeOH/H<sub>2</sub>O (0.1% TFA) to give **34h** as a

20 colourless glass. 38.2mg (56.6%).

<sup>1</sup>H NMR (DMSO-D<sub>6</sub> + CD<sub>3</sub>COOD, 300MHz) δ 1.5-1.7 (1H, m); 1.8-2.1 (5H + CH<sub>3</sub>COOH, m); 2.3-2.6 (3H + DMSO, m); 2.9-3.1 (1H, m); 3.2-4.1 (7H, m); 4.3-4.5 (1H, m); 6.5-6.7 (2H, m); 6.9-7.0 (1H, m); 7.05-7.25 (5H, m).

MS (ESP+) 474 (M+H)<sup>+</sup>.

25 Anal. Calcd for C<sub>24</sub>H<sub>31</sub>N<sub>3</sub>S<sub>2</sub>O<sub>3</sub> 1.4TFA C, 50.8; H, 5.16; N, 6.14

Found

C, 51.0; H, 5.3; N, 6.7

The starting material was prepared as described in a) immediately above.

30

- 91 -

Example 33 (see Scheme 40)

Preparation of

- a) (2S)-2-{2-Benzyl-4-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-benzoylamino}-4-methylsulfanylbutyric acid methyl ester (compound 35) and:
- 5 b) (2S)-2-{2-Benzyl-4-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-benzoylamino}-4-methylsulfanylbutyric acid (compound 35g)

a) Preparation of Compound 35

The title compound **35** was synthesised from methyl-2-bromo-4-nitro-benzoate using the  
10 same methodology as described in **Example 32** but using  $\text{Pd}_2(\text{dba})_3$  as a source of catalytic palladium in the benzylation reaction.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6 + \text{CD}_3\text{COOD}$ , 300MHz)  $\delta$  1.5-1.7(1H,m); 1.8-2.1(5H,m);  
2.3-2.6(3H+DMSO,m); 2.9-3.1(1H,m); 3.2-3.8(8H,m); 4.05(2H,m); 4.4-4.6(1H,m);  
6.4-6.6(2H,m); 7.0-7.35(6H,m)

15 MS (ESP+)  $m/z$  488(M+H) $^+$ , 325.

Anal Calcd for  $\text{C}_{25}\text{H}_{33}\text{N}_3\text{S}_2\text{O}_3 \cdot 2\text{HCl}$  C.53.6; H.6.29; N.7.5

Found C.53.5; H.6.5; N.7.3

b) Preparation of Compound 35g

20 Compound **35** (100mg, 0.18mmol; see a) above) was hydrolysed (analogously as for the equivalent step in **Example 32**) to give **35g** as a white solid, 85.8mg (67.3%).

$^1\text{H}$  NMR ( $\text{DMSO}-d_6 + \text{CD}_3\text{COOD}$ , 300MHz)  $\delta$  1.5-1.7(1H,m); 1.8-2.1(5H,m);  
2.3-2.6(3H+DMSO,m); 2.9-3.9(6H,m); 3.95-4.2(2H,m); 4.3-4.6(1H,m); 6.4-6.5(2H,m);  
7.0-7.3(6H,m)

25 MS (ESP+)  $m/z$  474(M+H) $^+$ , 325.

Anal Calcd for  $\text{C}_{24}\text{H}_{31}\text{N}_3\text{S}_2\text{O}_3 \cdot 1.3\text{TFA}$  C.51.4; H.5.24; N.6.76

Found C.51.2; H.5.4; N.6.7

Example 34 (see Scheme 41)

**(2S)-2-{2-Benzyl-5-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-benzoylamino}-4-methylsulfanylbutyric acid isopropyl ester** (compound 36)

The nitro compound **36b** was reduced to the corresponding aniline, coupled with the thioproline aldehyde **22b** using IPA as solvent and deprotected exactly analogously as for **Example 32** to give the title compound **36**.

$^1\text{H}$  NMR (DMSO- $\text{D}_6$ + $\text{CD}_3\text{COOD}$ , 300 $\text{MHz}$ )  $\delta$  1.0-1.3(6H,m); 1.5-1.7(1H,m); 1.8-2.1(5H,m); 2.3-2.6(3H+DMSO,m); 2.9-4.1(8H,m); 4.3-4.6(1H,m); 4.8-5.0(1H,m); 6.5-6.7(2H,m); 6.8-7.3(6H,m)

MS (ESP+)  $m/z$  516( $\text{M}+\text{H}$ ) $^+$ , 325.

Anal Calcd for  $\text{C}_{27}\text{H}_{37}\text{N}_3\text{S}_2\text{O}_3 \cdot 2\text{HCl}$

C, 55.1; H, 6.68; N, 7.14

Found

C, 54.9; H, 7.0; N, 7.1

Compound 36a

A solution of **34d** (25.24g, 62.78mmol) in MeOH (500mL) was treated with 2N NaOH (35mL, 70mmol). The resulting solution was then evaporated to dryness and the solids partitioned between  $\text{Et}_2\text{O}$  (200mL) and water (500mL). The aqueous was then acidified to pH2 with 2N HCl and extracted with EtOAc (2x250mL). The combined organics were washed with water (2x100mL), brine (100mL), filtered through phase separating paper and evaporated to give **36a** as a white solid, 23.57g (96.8%).

$^1\text{H}$  NMR (DMSO- $\text{D}_6$ , 300 $\text{MHz}$ )  $\delta$  1.8-2.2(5H,m); 2.3-2.6(2H+DMSO,m); 4.1-4.3(2H,m); 4.4-4.6(1H,m); 7.1-7.3(5H,m); 7.4-7.6(1H,m); 8.1-8.3(2H,m); 8.9-9.0(1H,m,  $\text{NHCO}$ )

MS (ESP-)  $m/z$  387( $\text{M}-\text{H}$ ) $^-$ .

Compound 36b

Sulphuryl chloride (5.0mL, 62mmol) was added to a stirred suspension of **36a** (19.2g, 50mmol) in IPA (500mL). The resulting mixture was then heated at reflux for 18hrs. The reaction mixture was then evaporated to 1/5 volume and partitioned between EtOAc (1L) and saturated  $\text{NaHCO}_3$  (aq) (500mL). The organics were then washed with water (200mL), brine (200mL), filtered through phase separating paper and evaporated to give **36b** as a white solid, 21.25g (100%)

$^1\text{H}$  NMR (DMSO- $\text{D}_6$ , 300 $\text{MHz}$ )  $\delta$  1.0-1.3(6H,m); 1.8-2.2(5H,m);

- 93 -

2.3-2.6(2H+DMSO.m):4.1-4.3(2H.m):4.4-4.6(1H.m):4.8-5.0(1H.m):7.1-7.3(5H.m);  
7.4-7.6(1H.m):8.1-8.3(2H.m):9.0(1H.m.NHCO)  
MS (ESP+) m/z 431(M+H)<sup>+</sup>.

5 Example 35 (see Scheme 42)

**(2S)-2-{2-Benzyl-5-[N-([2S,4S]-4-sulfanylpyrrolidin-2-ylmethyl)-N-(3-methoxypropionyl)-amino]-benzoylamino}-4-methylsulfanylbutyric acid isopropyl ester** (compound 37)

- 10 Starting material **37b** was deprotected using the same methodology for the equivalent step described in Example 32 to give the title compound **37**.

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>+CD<sub>3</sub>COOD,300MHz) δ1.0-1.3(6H.m):1.5-1.7(1H.m);  
1.8-2.1(5H.m):2.2-2.6(5H+DMSO.m):2.9-3.95(10H.m):4.0-4.2(3H.m),  
4.4-4.6(1H.m):4.8-5.0(1H.m):7.0-7.5(8H.m)

- 15 MS (ESP+) m/z 602 (M+H)<sup>+</sup>.

Anal Calcd for C <sub>31</sub> H <sub>43</sub> N <sub>3</sub> S <sub>2</sub> O <sub>5</sub> ·1.5HCl	C,56.7;H,6.83;N,6.4
Found	C,56.7;H,7.0;N,6.0

The starting material was prepared as follows.

- 20 EEDQ (530mg,2.15mmol) was added to a stirred solution of **36d** (1.5g,2.15mmol; see Example 34) and 3-methoxy propionic acid (220mL, 2.36mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15mL). The mixture was left to stir 18hrs at RT then evaporated. The residues were then partitioned between 1N citric acid(aq) (200mL) and EtOAc (100mL). The organics were washed with saturated NaHCO<sub>3</sub> (aq) (50mL), water(50mL) and brine(50mL), filtered through phase  
25 separating paper and evaporated to give a pale yellow gum. This was then purified by flash chromatography on SiO<sub>2</sub> (Merck 9385) eluting a gradient of 0-50% EtOAc/i-Hexane. Appropriate fractions were filtered and evaporated to give starting material **37b** as a colourless gum,1.14g(67.7%).  
MS (ESP+) m/z 786 (M+H)<sup>+</sup>.

30

Example 36 (see Scheme 43)

## Preparation of

- a) N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-1-yl-ethyl)-butyramide (compound 56) and:
- 5 b) N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-N-(2-naphthalen-1-yl-ethyl)-2-pyridin-3-yl-acetamide (compound 57)

a) Preparation of compound 56

- The method described in Example 23 for the synthesis of compound (6) was used to
- 10 prepare compound (56) as set out in Scheme 43.
- NMR data in CDCl<sub>3</sub>  $\delta$  0.91(s, 9H), 1.5(m, 1H), 1.75(m, 1H), 1.82(d, 1H), 1.91(d, 1H), 2.52(m, 1H), 2.92(m, 1H), 3.33(m, 3H), 3.72(m, 4H), 4.15(m, 1H), 7.26(d, 1H), 7.41(t, 1H), 7.56(m, 2H), 7.8(d, 1H), 7.9(2d, 2H), 9.08(br.s, 1H).
- Micro Analysis: %Theory C64.2, H7.97, N6.5
- 15 (1.00 HCl . 0.5H<sub>2</sub>O %Found C64.4, H7.90, N6.3

Starting material compound (54) was synthesised analogously with Example 23 using the appropriate intermediates:

## Compound (52).

- 20 NMR data in CDCl<sub>3</sub>  $\delta$  1.00(2s, 9H), 1.46(d, 9H), 1.95(m, 2H), 2.4(m, 2H), 3.3(m, 4H), 3.7(m, 3H), 4.00(m, 3H), 4.57(d, 2H), 5.22(2d, 2H), 5.90(m, 1H), 7.24-8.4(m, 7H).

## Compound (54).

- NMR data in CDCl<sub>3</sub>  $\delta$  1.00(2s, 9H), 1.35(m, 1H), 1.49(s, 9H), 1.89(br.s, 1H), 1.95(d, 1H), 2.3(m, 1H), 2.32(d, 1H), 2.88(2q, 1H), 3.1-3.9(m, 9H), 7.25-8.31(m, 7H),
- 25

b) Preparation of Compound 57

- The method described in Example 24 for the synthesis of compound (27) was used in a similar manner to prepare compound (57).
- NMR data in CDCl<sub>3</sub>  $\delta$  1.2(m, 1H), 2.00(m, 1H), 2.6(m, 2H), 3.15-4.40(m, 10H), 7.28-
- 30 8.70(m, 11H), 9.4(br.s, 1H).



- 95 -

Micro Analysis:                      %Theory C56.0, H6.20, N8.17  
(2HCl. 2H<sub>2</sub>O)                      %Found C56.4, H6.46, N7.70

Starting material compound(55) was synthesised analogously with Example 24 using  
5 appropriate intermediates:

Compound (53).

NMR data in CDCl<sub>3</sub> δ 1.48(s, 9H), 1.84(m, 1H), 2.42(m, 1H), 2.87-3.45(m, 5H), 3.63-  
4.26(m, 7H), 4.55(d, 2H), 5.22(2d, 2H), 5.9(m, 1H), 7.1-8.7(m, 11H).

Compound (55).

10 NMR data in CDCl<sub>3</sub> δ 1.34(m, 1H), 1.5(s, 9H), 1.95(m, 1H), 2.32(m, 2H), 2.72-4.00(m,  
10H), 7.1-8.6(m, 11H).

Example 37 (see Scheme 44)

Preparation of

- 15 a) **N-(2,2-Diphenyl-ethyl)-N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-  
butyramide** (compound 67);  
b) **N-(2,2-Diphenyl-ethyl)-N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-  
dimethyl-butyramide** (compound 68);  
c) **N-(2,2-Diphenyl-ethyl)-N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-2-pyridin-  
20 3-yl-acetamide** (compound 69) and;  
d) **N-(2,2-Diphenyl-ethyl)-1-oxy-N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-6-  
methoxy-nicotinamide** (compound 70).

a) Preparation of Compound 67

- 25 The method described in Example 23 for the synthesis of compound (6) was used in an  
analogous manner to prepare compound (67) using appropriate intermediates - see Scheme  
44.

NMR data in DMSO-d<sub>6</sub> δ 0.75(m, 6H), 1.55(m, 1H), 1.87(m, 2H), 2.05-2.45(m, 1H),  
3.05(m, 1H), 3.25-3.70(m, 6H), 4.05(m, 2H), 4.20-4.55(m, 1H), 7.30(m, 10H), 8.80-

30 9.80(2br.s, 2H)

- 96 -

Micro Analysis: %Theory C63.9. H7.82. N6.21

(1.00HCl, 1.00H<sub>2</sub>O) %Found C64.1. H7.70. N6.00

Compound (58).

NMR data in CDCl<sub>3</sub>  $\delta$  1.50(s, 9H), 1.77(m, 1H), 2.40(m, 1H), 2.75(m, 1H), 3.00(m, 1H),

5 3.14(q, 1H), 3.24(d, 2H), 3.67(m, 1H), 3.93(m, 1H), 4.10(m, 2H), 4.54(d, 2H), 5.25(m, 2H),  
5.90(m, 1H), 7.25(m, 10H)

Compound (59).

NMR data in CDCl<sub>3</sub>  $\delta$  0.85(m, 6H), 1.48(m, 9H), 1.80(m, 2H), 2.10(m, 2H), 2.40(m, 1H),

2.80-4.35(m, 9H), 4.55(m, 2H), 5.25(m, 2H), 5.90(m, 1H), 7.25(m, 10H)

10 Compound (63).

NMR data in CDCl<sub>3</sub>  $\delta$  0.85(2d, 6H), 1.24(m, 1H), 1.48(s, 9H), 1.68(m, 1H), 1.81(d, 1H),

1.95-2.35(m, 3H), 2.75-3.65(m, 6H), 3.90-4.55(m, 3H), 7.25(m, 10H)

b) Preparation of Compound 68

15 Similarly compound (68) was synthesised from compound (60) as set out in Scheme 44.

Compound (68)

NMR data in DMSO-d<sub>6</sub>  $\delta$  0.85(m, 9H), 1.55(m, 1H), 1.74-2.27(m, 2H), 2.37(m, 1H),

3.05(m, 1H), 3.45(m, 6H), 4.05(m, 2H), 4.18-4.55(m, 1H), 7.28(m, 10H), 8.90-9.90(m, 2H)

Micro Analysis: %Theory C64.6. H8.02. N6.02

20 (1.0HCl, 1.0H<sub>2</sub>O) %Found C64.8. H8.30. N5.70

Compound (60).

NMR data in CDCl<sub>3</sub>  $\delta$  0.93(m, 9H), 1.50(s, 9H), 1.82(m, 2H), 2.35(m, 3H), 2.90-4.35(m,  
8H), 4.55(m, 2H), 5.25(m, 2H), 5.90(m, 1H), 7.25(m, 10H).

Compound (64).

25 NMR data in CDCl<sub>3</sub>  $\delta$  0.93(s, 9H), 1.24(m, 1H), 1.48(s, 9H), 1.80(q, 1H), 2.23(d, 1H),  
2.30(m, 1H), 2.75-3.70(m, 6H), 3.90-4.60(m, 3H), 7.25(m, 10H).

c) Preparation of Compound 69

Compound (69) was synthesised from compound (61) (see Scheme 44) analogously with

30 the procedure described in Example 24 for the preparation of compound (27).

Compound (69).

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- 97 -

NMR data in  $\text{CDCl}_3$   $\delta$  1.95(m,1H), 2.40(m,1H), 2.60(m,1H), 3.15-4.50(m,11H), 7.28(m,10H), 7.67(m,1H), 8.05(m,1H), 8.50(m,1H), 8.71(m,1H), 9.10-10.20(br.d, 2H).

Micro Analysis: %Theory C55.1, H5.51, N7.01

(2.0 HCl, 0.75 TFA, 0.5  $\text{H}_2\text{O}$ ) %Found C55.0, H5.60, N6.90

5 Compound (61).

NMR data in  $\text{CDCl}_3$   $\delta$  1.47(s, 9H), 1.80(m,1H), 2.30-4.65(m,14H), 5.23(m, 2H), 5.90(m,1H), 7.25(m,12H), 8.10-8.55(m, 2H).

Compound (65).

NMR data in  $\text{CDCl}_3$   $\delta$  1.25(m,1H), 1.48(s, 9H), 2.30(m,1H), 2.70-4.55(m,12H),

10 7.30(m,12H), 8.28(2d,1H), 8.45(m,1H).

d) Preparation of Compound 70

Similarly compound (70) was synthesised from compound (62) using appropriate intermediates.

15 NMR data in  $\text{CDCl}_3$   $\delta$  1.67(m,1H), 2.15(d,1H), 2.47(m,1H), 3.16(br.s, 1H), 3.50(m, 2H), 3.85-4.40(m, 8H), 5.22(br.s,1H), 6.56(d,1H), 7.00-7.35(m,11H), 7.90(s,1H), 8.85-10.75(2br.s, 2H)

Micro Analysis %Theory C57.2, H5.91, N7.70

(2.0 HCl, 0.5  $\text{H}_2\text{O}$ ) %Found C57.5, H5.60, N7.30

20

Compound (62).

NMR data in  $\text{CDCl}_3$   $\delta$  1.50(s, 9H), 1.60(m,1H), 2.47(m,1H), 3.00-4.50(m,12H), 4.58(d, 2H), 5.25(m, 2H), 5.90(m,1H), 6.53(d,1H), 6.95(m,1H), 7.25(m,11H).

Compound (66).

25 NMR data in  $\text{CDCl}_3$   $\delta$  1.20(m,1H), 1.45(s, 9H), 2.30(m,1H), 2.66(m,1H), 3.00-3.45(m, 4H), 3.55(m,1H), 3.95-4.25(m, 5H), 4.47(m,1H), 6.55(d,1H), 7.25(m,11H), 7.65(m,1H).

Example 38 (see Scheme 45)

Preparation of

30 a) N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-N-(2-naphthalen-2-yl-ethyl)-butyramide (compound 80);

SUBSTITUTE SHEET (RULE 26)

- 98 -

- b) N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-2-yl-ethyl)-butyramide (compound 81);
- c) N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-N-(2-naphthalen-2-yl-ethyl)-2-pyridin-3-yl-acetamide (compound 82) and;
- 5 d) N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-2-(4-methoxy-phenyl)-N-(2-naphthalen-2-yl-ethyl)-acetamide (compound 83).

a) Preparation of Compound 80

The method described in Example 23 for the synthesis of compound (6) was used to  
10 prepare compound (80).

NMR data in DMSO-d<sub>6</sub>  $\delta$  0.75(m, 6H), 0.87(d, 1H), 1.65(m, 1H), 1.92(m, 1H), 2.02(d, 1H), 3.03(m, 3H), 3.20-3.80(m, 9H), 7.48(m, 3H), 7.75(d, 1H), 7.85(m, 3H), 8.90-9.90(br.d, 2H)

15 Micro Analysis:        %Theory C64.9, H7.68, N6.88  
                             %Found C64.9, H7.50, N6.80  
(1.00 HCl)

Starting material compound (76) was synthesised analogously with Example 23 using appropriate intermediates - see Scheme 45.

20

Compound (71).

NMR data in CDCl<sub>3</sub>  $\delta$  1.50(s, 9H), 1.85(m, 1H), 2.50(m, 1H), 2.80(m, 1H), 3.00(m, 5H), 3.20(m, 1H), 3.65(m, 1H), 4.00(m, 1H), 4.10(m, 1H), 4.53(d, 2H), 5.20(m, 2H), 5.90(m, 1H), 7.32(m, 1H), 7.42(m, 2H), 7.63(s, 1H), 7.80(m, 3H).

25

Compound (72).

NMR data in CDCl<sub>3</sub>  $\delta$  0.90(m, 7H), 1.00-2.60(m, 14H), 3.00(m, 2H), 3.10-4.20(m, 7H), 4.60(m, 2H), 5.25(m, 2H), 5.90(m, 1H), 7.30-7.50(m, 3H), 7.60(m, 1H), 7.80(m, 3H).

30

- 99 -

Compound (76).

NMR data in  $\text{CDCl}_3$   $\delta$  0.90(m, 6H), 1.10-2.50(m, 15H), 2.80-3.80(m, 9H), 7.26-7.50(m, 3H), 7.60(m, 1H), 7.80(m, 3H)

5 b) Preparation of Compound 81

Compound (81) was synthesised from compound (73) as set out in Scheme 45 in a similar manner to preparation of compound 80 (see above).

NMR data in  $\text{DMSO-d}_6$   $\delta$  1.08(d, 9H), 1.80(m, 1H), 2.15(m, 2H), 2.65(m, 1H), 3.00-  
10 4.00(m, 10H), 7.63(m, 3H), 7.90(s, 1H), 8.03(m, 3H), 9.50(br.d, 2H).

Micro Analysis:                      %Theory C64.9, H7.93, N6.58  
(1.0HCl.0.25H<sub>2</sub>O)                      %Found C64.8, H8.10, N6.50

Compound (73).

15 NMR data in  $\text{CDCl}_3$   $\delta$  1.00(m, 9H), 1.47(s, 9H), 1.80-2.55(m, 4H), 3.00(m, 2H), 3.10-  
4.20(m, 8H), 4.60(d, 2H), 5.25(m, 2H), 5.90(m, 1H), 7.30-7.85(m, 7H)

Compound (77).

NMR data in  $\text{DMSO-d}_6$  (100°C)  $\delta$  0.95(m, 9H), 1.35-1.75(m, 9H), 2.15(s, 2H),  
20 2.40(m, 1H), 2.60-3.90(m, 12H), 7.40(m, 3H), 7.70(m, 1H), 7.80(m, 3H).

c) Preparation of Compound 82

Compound (82) was synthesised from compound (74) as set out in Scheme 45 by a similar procedure to that described in Example 24 for the preparation of compound (27).

25

Compound (82).

NMR data in  $\text{DMSO-d}_6$   $\delta$  1.65(m, 1H), 2.90-4.15(m, 14H), 7.35-8.90(m, 11H), 9.50(br.d, 2H).

30 Micro Analysis:                      %Theory C51.9, H5.19, N6.99  
(2.0HCl, 1.0TFA, 0.5H<sub>2</sub>O)                      %Found C52.2, H5.40, N, 7.00

SUBSTITUTE SHEET (RULE 26)

- 100 -

Compound (74).

NMR data in DMSO-d<sub>6</sub> (100°C)  $\delta$  1.45-1.75(m, 10H), 2.85-3.85(m, 11H), 4.03(m, 1H), 4.20(m, 1H), 4.45-4.65(m, 2H), 5.20(m, 2H), 5.90(m, 1H), 7.23(m, 1H), 7.45(m, 4H), 7.67(s, 1H), 7.80(m, 3H), 8.35(m, 2H).

5

Compound (78)

NMR data in DMSO-d<sub>6</sub> (100°C)  $\delta$  1.30-1.75(m, 9H), 2.40(m, 1H), 2.55-3.90(m, 14H), 7.10-8.45(m, 11H).

10 d) Preparation of Compound 83

Similarly compound (83) was synthesised from compound (75) using appropriate intermediates as set out in Scheme 45.

Compound (85).

15 NMR data in DMSO-d<sub>6</sub>  $\delta$  1.65(m, 1H), 2.95(m, 2H), 3.08(m, 1H), 3.25-4.00(m, 13H), 6.80(m, 2H), 7.06(2d, 2H), 7.47(m, 3H), 7.68(d, 1H), 7.85(m, 3H), 9.35(br.d, 2H).

Micro Analysis: %Theory C62.7, H6.57, N5.62

(1.5 HCl.0.5H<sub>2</sub>O) %Found C62.4, H6.50, N5.40

20

Compound (75).

NMR data in DMSO-d<sub>6</sub> (100°C)  $\delta$  1.45(s, 9H), 1.75(m, 1H), 2.75-3.85(m, 14H), 4.00(m, 1H), 4.14(m, 1H), 4.45-4.65(m, 2H), 5.20(m, 2H), 5.90(m, 1H), 6.80(m, 2H), 7.05(m, 2H), 7.33(m, 1H), 7.45(m, 2H), 7.63(s, 1H), 7.80(m, 3H).

25

Compound (79).

NMR data in DMSO-d<sub>6</sub> (100°C)  $\delta$  1.30-1.75(m, 9H), 2.35(m, 1H), 2.60-3.90(m, 17H), 6.78(m, 2H), 7.05(m, 2H), 7.40(m, 3H), 7.65(m, 1H), 7.80(m, 3H).

30

- 101 -

Example 39 (see scheme 46)

Preparation of

a) (2S)-2-({2-phenyl-4-[(2S,4S)-4-sulfanyl-pyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino)-4-methylsulfanyl-butyric acid methyl ester (compound 38)

5 and;

b) (2S)-2-({2-phenyl-4-[(2S,4S)-4-sulfanyl-pyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino)-4-methylsulfanyl-butyric acid (compound 38f).

a) Preparation of Compound 38

Methyl -2-bromo-4-nitro-benzoate was coupled with phenyl boronic acid (analogously as  
10 for the equivalent step in **Example 30**) then coupled and deprotected using the same methodology as previously described for **Example 32** to give the title compound **38**.

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>, 250MHz) δ 1.35-1.75(3H,m); 1.8(3H,s); 1.9-2.2(2H,m);  
2.25-2.5(2H+DMSO,m); 2.75-3.9(10H,m); 4.0-4.25(1H,m); 5.0-5.9(5H,bs,H<sub>2</sub>O);  
6.3-6.6(2H,m); 7.0-7.3(7H,m); 7.95(1H,m); 9.2-9.8(2H,bd).

15 MS (ESP+) m/z 474 (M+H)<sup>+</sup>, 311, 196.

Anal. Calcd for C<sub>24</sub>H<sub>31</sub>N<sub>3</sub>O<sub>3</sub>S<sub>2</sub>·2HCl·1.5H<sub>2</sub>O

C, 50.3; H, 6.3; N, 7.3

Found

C, 50.4; H, 6.1; N, 7.3

b) Preparation of Compound 38f

20 Compound **38** was hydrolysed to the corresponding acid (analogously as for the equivalent step in **Example 33**) to give **38f**.

<sup>1</sup>H NMR (DMSO-D<sub>6</sub>+CD<sub>3</sub>COOD, 300MHz) δ 1.5-1.9(3H+CD<sub>3</sub>COOD,m); 1.95(3H,s);  
2.05-2.35(2H,m); 2.4-2.6(2H+DMSO,m); 3.0-3.1(1H,m); 3.2-3.9(4H,m); 4.2-4.3(1H,m); 6.5-  
6.7(2H,m); 7.2-7.4(6H,m).

25 MS (ESP+) m/z 460 (M+H)<sup>+</sup>, 311.

Anal. Calcd for C<sub>23</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>S<sub>2</sub>·1.35TFA

C, 50.3; H, 4.99; N, 6.85

Found

C, 50.2; H, 5.1; N, 6.8

Example 40**Pharmaceutical compositions**

The following illustrate representative pharmaceutical dosage forms of the invention as defined herein (the active ingredient being termed "Compound X"). for  
5 therapeutic or prophylactic use in humans:

(a)	<u>Tablet I</u>	<u>mg/tablet</u>
	Compound X.....	100
	Lactose Ph.Eur.....	182.75
10	Croscarmellose sodium.....	12.0
	Maize starch paste (5% w/v paste).....	2.25
	Magnesium stearate.....	3.0
(b)	<u>Tablet II</u>	<u>mg/tablet</u>
15	Compound X.....	50
	Lactose Ph.Eur.....	223.75
	Croscarmellose sodium.....	6.0
	Maize starch.....	15.0
	Polyvinylpyrrolidone (5% w/v paste).....	2.25
20	Magnesium stearate.....	3.0
(c)	<u>Tablet III</u>	<u>mg/tablet</u>
	Compound X.....	1.0
	Lactose Ph.Eur.....	93.25
25	Croscarmellose sodium.....	4.0
	Maize starch paste (5% w/v paste).....	0.75
	Magnesium stearate.....	1.0

30



- 103 -

	(d)	<u>Capsule</u>	<u>mg/capsule</u>
		Compound X.....	10
		Lactose Ph.Eur.....	488.5
		Magnesium.....	1.5
5			
	(e)	<u>Injection I</u>	<u>(50 mg/ml)</u>
		Compound X.....	5.0% w/v
		1M Sodium hydroxide solution.....	15.0% v/v
		0.1M Hydrochloric acid	
10		(to adjust pH to 7.6)	
		Polyethylene glycol 400.....	4.5% w/v
		Water for injection to 100%	
	(f)	<u>Injection II</u>	<u>(10 mg/ml)</u>
15		Compound X.....	1.0% w/v
		Sodium phosphate BP.....	3.6% w/v
		0.1M Sodium hydroxide solution.....	15.0% v/v
		Water for injection to 100%	
20	(g)	<u>Injection III</u>	<u>(1mg/ml, buffered to pH6)</u>
		Compound X.....	0.1% w/v
		Sodium phosphate BP.....	2.26% w/v
		Citric acid.....	0.38% w/v
		Polyethylene glycol 400.....	3.5% w/v
25		Water for injection to 100%	
	(h)	<u>Aerosol I</u>	<u>mg/ml</u>
		Compound X.....	10.0
		Sorbitan trioleate.....	13.5
30		Trichlorofluoromethane.....	910.0
		Dichlorodifluoromethane.....	490.0

SUBSTITUTE SHEET (RULE 26)

- 104 -

5	(i)	<u>Aerosol II</u>	<u>mg/ml</u>
		Compound X.....	0.2
		Sorbitan trioleate.....	0.27
		Trichlorofluoromethane.....	70.0
		Dichlorodifluoromethane.....	280.0
		Dichlorotetrafluoroethane.....	1094.0
10	(j)	<u>Aerosol III</u>	<u>mg/ml</u>
		Compound X.....	2.5
		Sorbitan trioleate.....	3.38
		Trichlorofluoromethane.....	67.5
		Dichlorodifluoromethane.....	1086.0
		Dichlorotetrafluoroethane.....	191.6
15	(k)	<u>Aerosol IV</u>	<u>mg/ml</u>
		Compound X.....	2.5
		Soya lecithin.....	2.7
		Trichlorofluoromethane.....	67.5
		Dichlorodifluoromethane.....	1086.0
20		Dichlorotetrafluoroethane.....	191.6
25	(l)	<u>Ointment</u>	<u>ml</u>
		Compound X.....	40 mg
		Ethanol.....	300 µl
		Water.....	300 µl
		1-Dodecylazacycloheptan-2-one.....	50 µl
		Propylene glycol.....	to 1 ml

Note

30 The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means.

**SUBSTITUTE SHEET (RULE 26)**

- 105 -

for example to provide a coating of cellulose acetate phthalate. The aerosol formulations (h)-(k) may be used in conjunction with standard, metered dose aerosol dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80.

5 polyglycerol oleate or oleic acid.

Example 41 (see Scheme 47)

**Preparation of**

- a) (2S)-4-Carbamoyl-2-({2-phenyl-5-[(2S,4S)-4-sulfanyl-pyrrolidin-2-ylmethyl]-  
10 amino]-phenylcarbonyl}-amino)-butyric acid (compound 39e); and  
b) (2S)-4-Carbamoyl-2-({2-phenyl-5-[(2S,4S)-4-sulfanyl-pyrrolidin-2-ylmethyl]-  
amino]-phenylcarbonyl}-amino)-butyric acid methyl ester (compound 39)

a) Preparation of Compound 39

15 Compound 39a

**32a** (1.5g, 6.2mmol) was coupled with L-Glutamine methyl ester (analogously as for the equivalent step in **Example 30**) to give compound **39a** as a white solid 1.2g (50.5%)  
MS (ESP)+ m/z 386 (M+H)+.

Compound 39

- 20 **39a** was reduced, coupled with the aldehyde (**22b**) and selectively deprotected using the same methodology as previously described for **Example 32** to give the title compound **39**.  
MS (ESP+) m/z 471 (M+H)+.

Anal. Calcd for C<sub>24</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub>S.3HCl.0.25H<sub>2</sub>O

C, 49.3; H, 5.8; N, 9.6

Found

C, 49.2; H, 5.9; N, 9.2

- 25 b) Preparation of Compound 39e

**39** was hydrolysed (analogously as for the equivalent step in **Example 32**) to give the title compound **39e**.

MS (ESP-) m/z 455 (M-H)-.

Anal. Calcd for C<sub>23</sub>H<sub>28</sub>N<sub>4</sub>O<sub>4</sub>S.2TFA

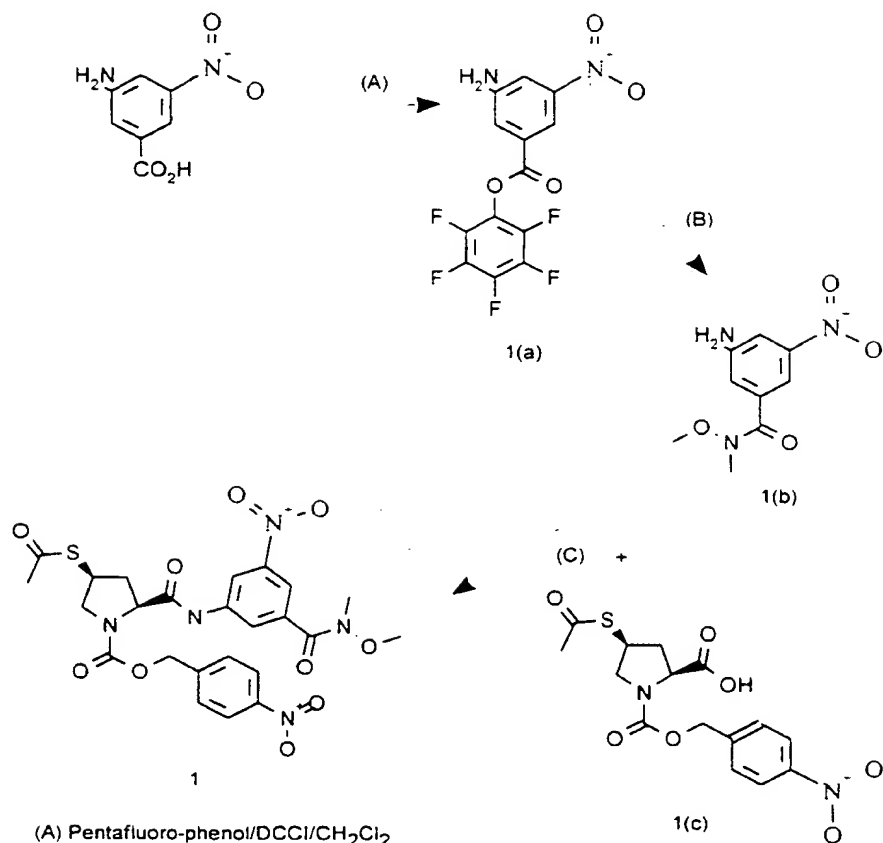
C, 47.4; H, 4.4; N, 8.2

- 30 Found

C, 47.0; H, 4.5; N, 7.9

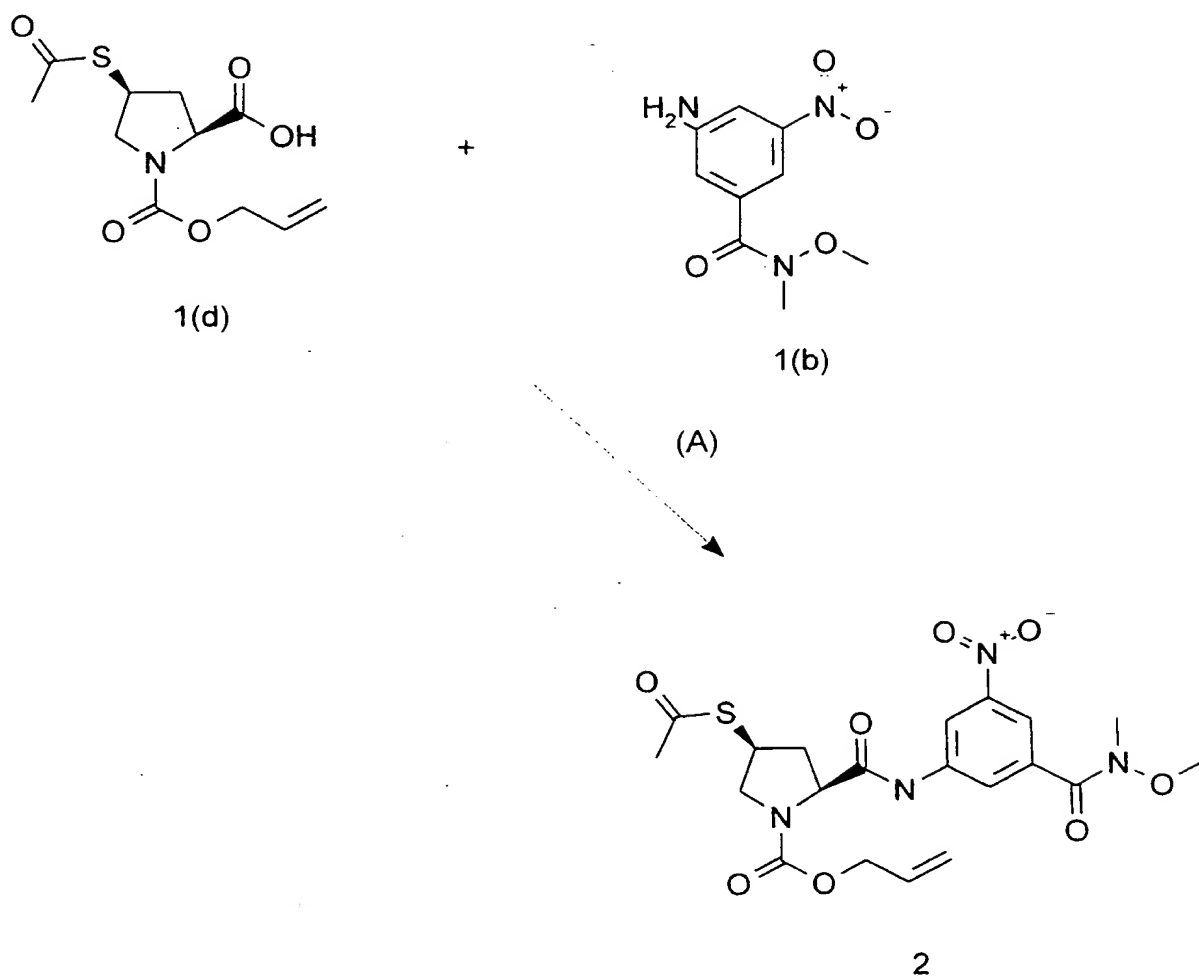
- 106 -

Scheme 1

(A) Pentafluoro-phenol/DCCl/CH<sub>2</sub>Cl<sub>2</sub>(B) N,O -Dimethylhydroxylamine/Triethylamine/CH<sub>2</sub>Cl<sub>2</sub>(C) EEDQ/CH<sub>2</sub>Cl<sub>2</sub>

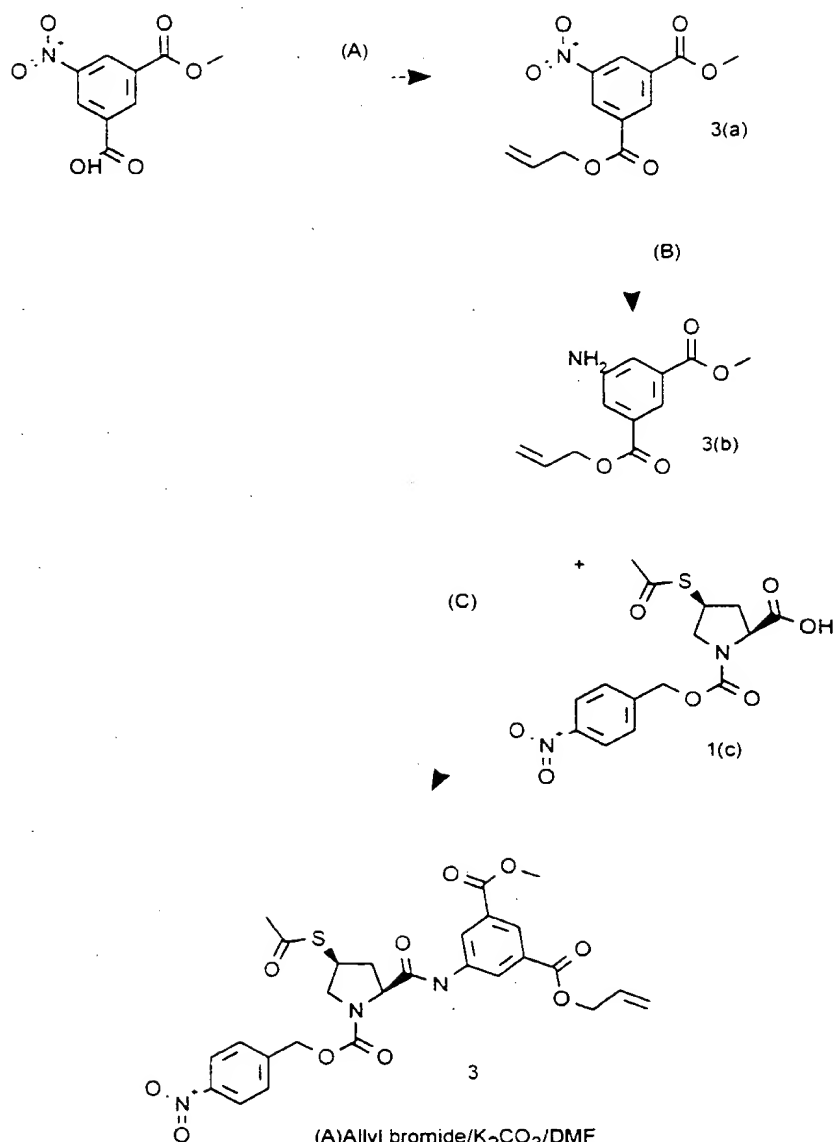
- 107 -

Scheme 2

(A) EEDQ/CH<sub>2</sub>Cl<sub>2</sub>

- 108 -

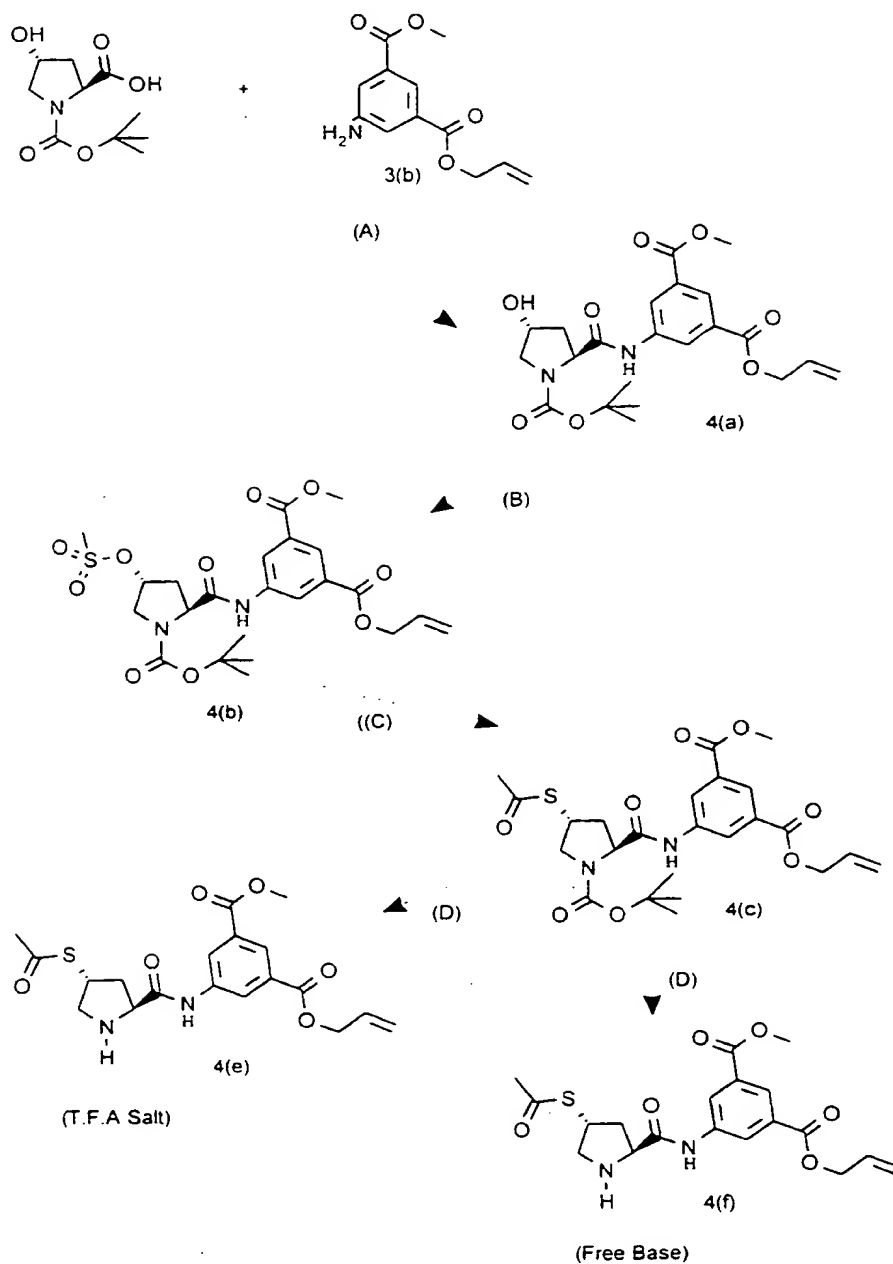
Scheme 3



(A) Allyl bromide/ $K_2CO_3$ /DMF  
(B) Tin(II) chloride dihydrate/MeOH/Reflux  
(C) EEDQ/ $CH_2Cl_2$

- 109 -

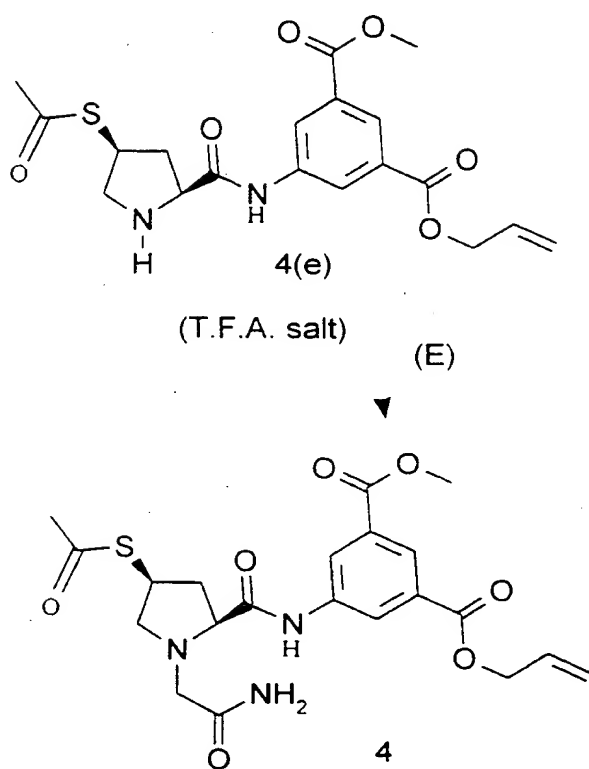
Scheme 4



SUBSTITUTE SHEET (RULE 26)

- 110 -

Scheme 4 cont.



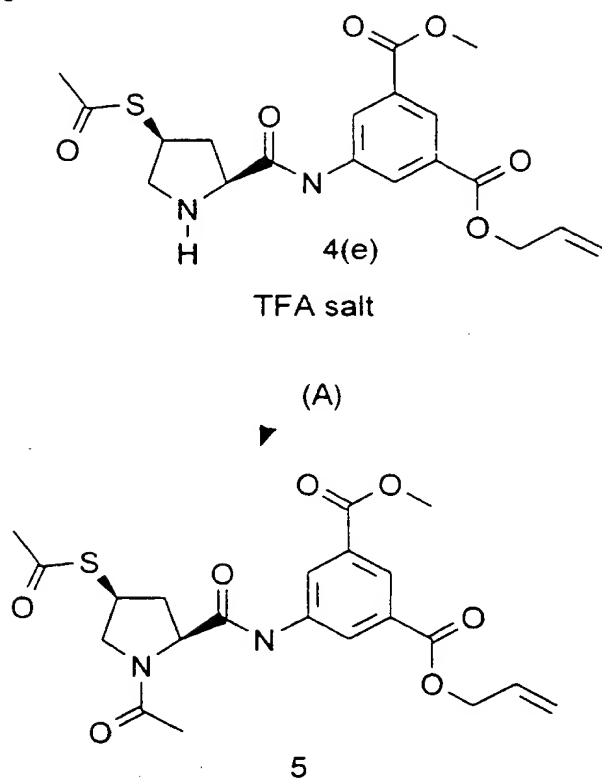
- (A) EEDQ/CH<sub>2</sub>Cl<sub>2</sub>
- (B) Methanesulphonyl chloride/triethylamine/CH<sub>2</sub>Cl<sub>2</sub>
- (C) Potassium thioacetate/acetone
- (D) T.F.A.
- (E) Iodoacetamide/Sodium Bicarbonate/DMF

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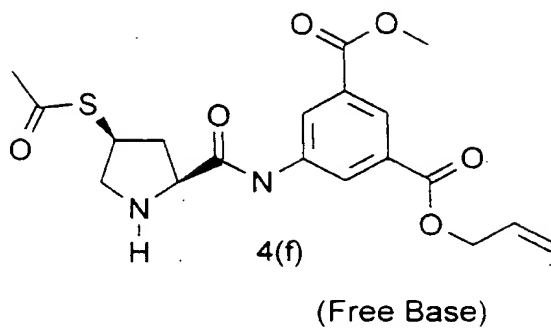
- 111 -

Scheme 5

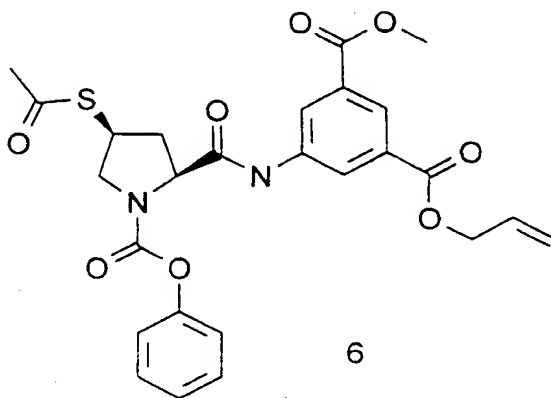
(A) Acetic anhydride/triethylamine/ $\text{CH}_2\text{Cl}_2$

- 112 -

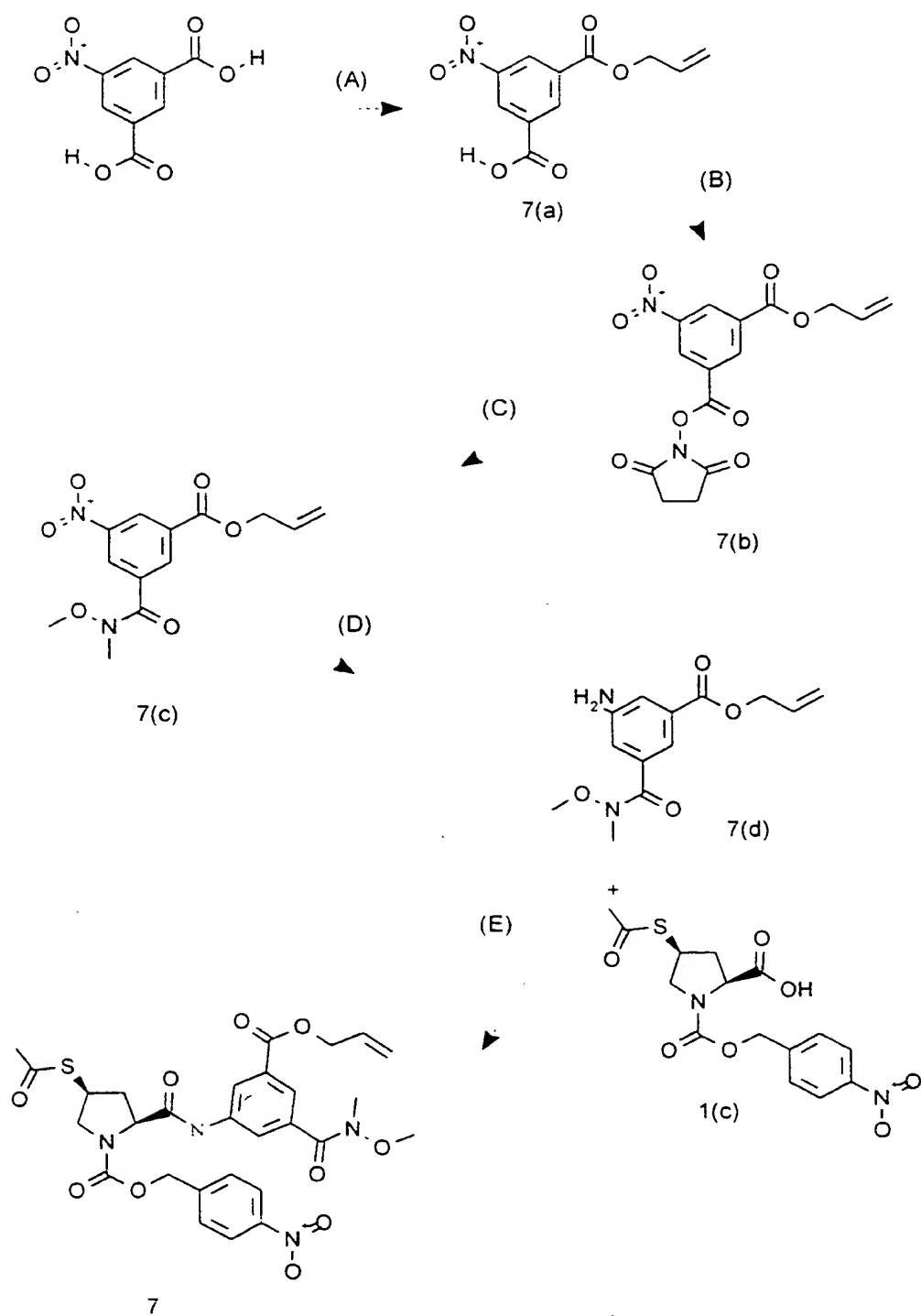
Scheme 6



(A)

(A) Phenyl chloroformate/triethylamine/ $\text{CH}_2\text{Cl}_2$

Scheme 7



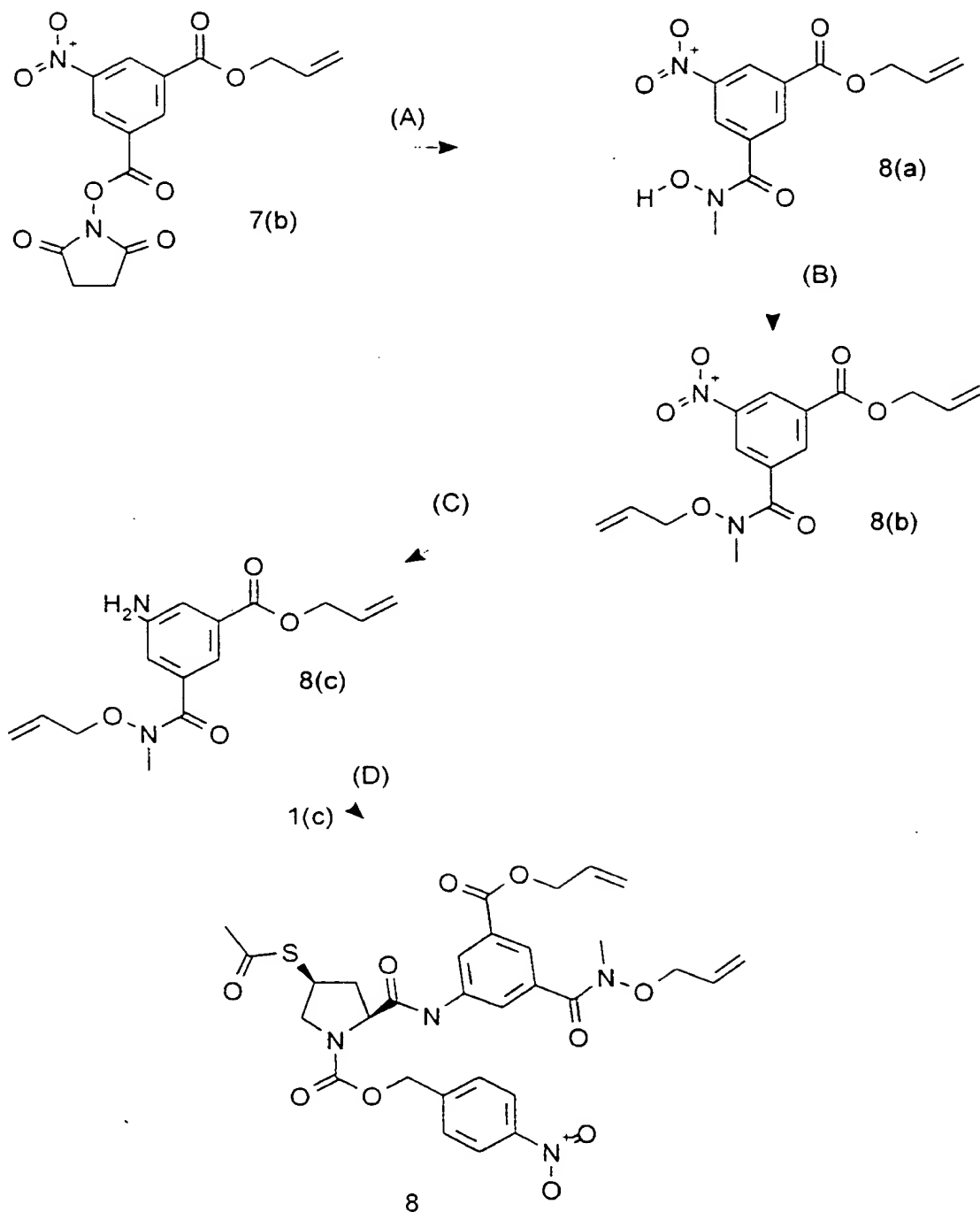
## Scheme 7(cont.)

- (A) Allyl bromide/potassium carbonate/DMA/90deg./4hrs  
(B) DCCI/N-Hydroxysuccinimide/ $\text{CH}_2\text{Cl}_2$ /R.T./3.5hrs.  
(C) N,O-Dimethylhydroxylamine HCl/Triethylamine/5deg./16hrs.  
(D) Tin(II) Chloride/Methanol/Reflux/1hr  
(E) EEDQ/ $\text{CH}_2\text{Cl}_2$ /R.T./16hrs.

120

SS

Scheme 8



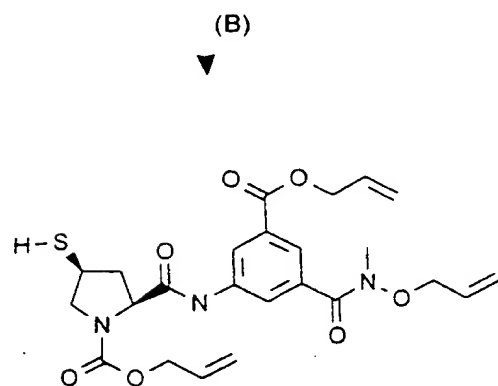
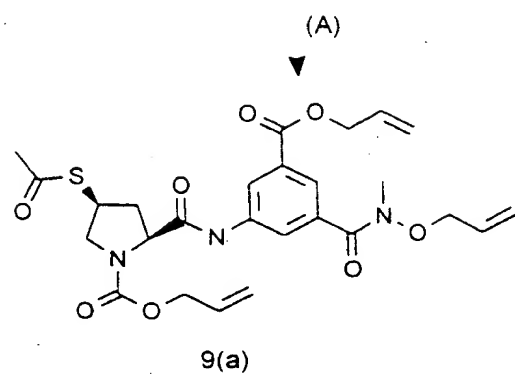
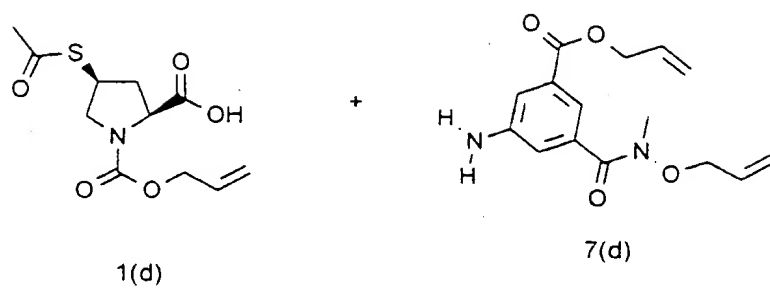
(A) N-Methylhydroxylamine HCl./Triethylamine/ $\text{CH}_2\text{Cl}_2$ /5deg./16hrs.

(B) Allyl bromide/Potassium carbonate/R.t./DMF/3hrs.

(C) Tin(II) chloride/Ethyl acetate/70Deg.

SUBSTITUTE SHEET (RULE 26)

Scheme 9

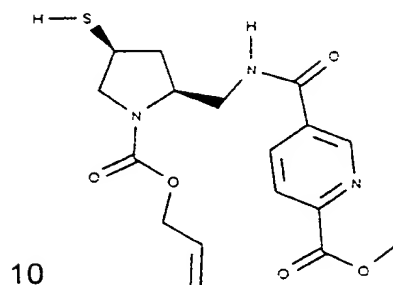
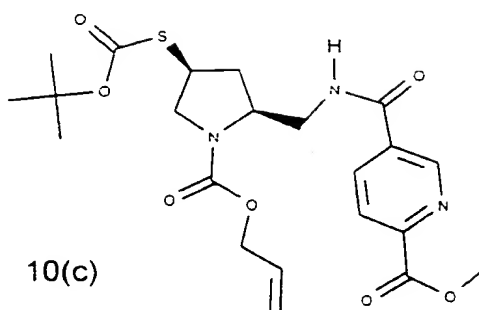
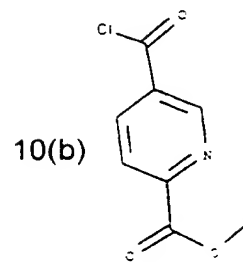
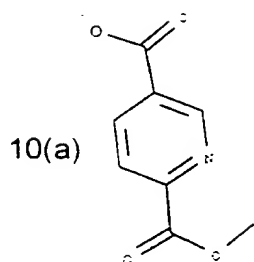


9

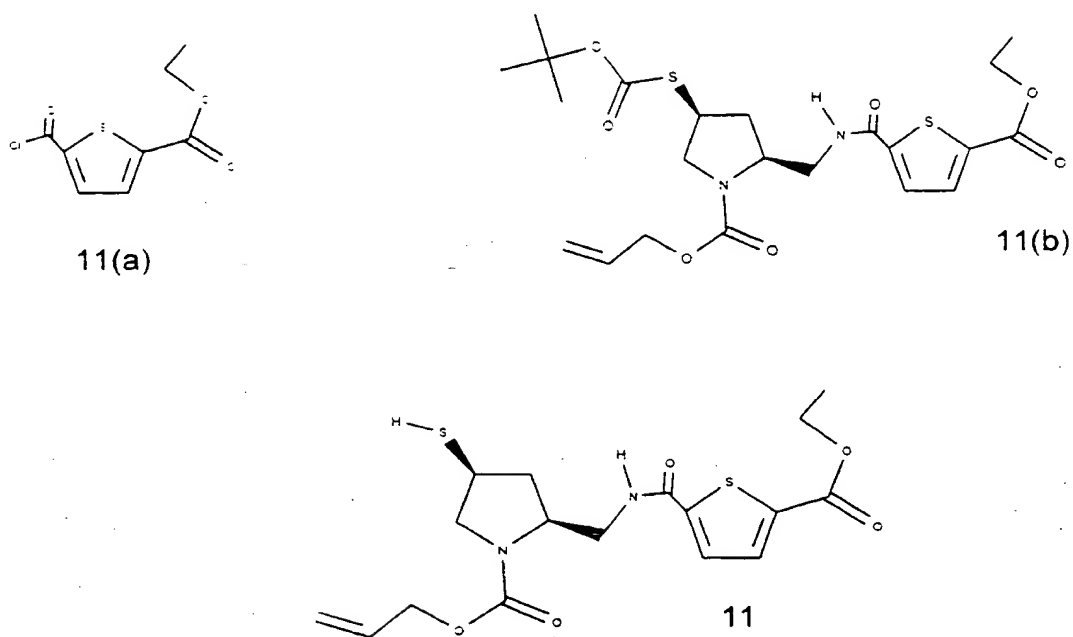
(A) EEDQ/CH<sub>2</sub>Cl<sub>2</sub>

(B) 0.1M Sodium hydroxide/Allyl alcohol/R.t.

## SCHEME 10



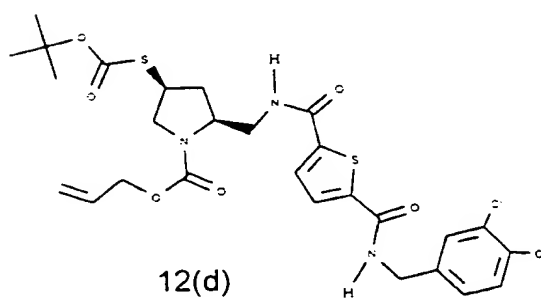
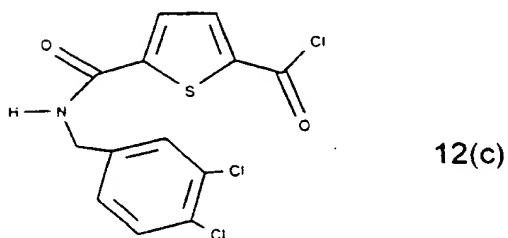
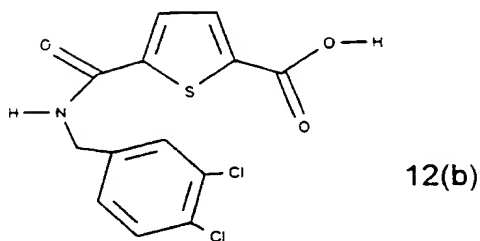
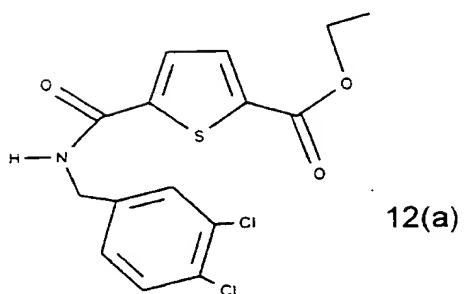
## SCHEME 11





- 119 -

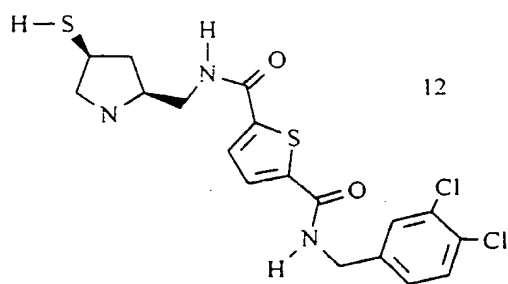
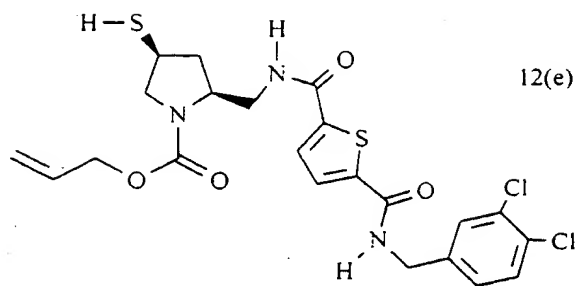
## SCHEME 12



SUBSTITUTE SHEET (RULE 26)

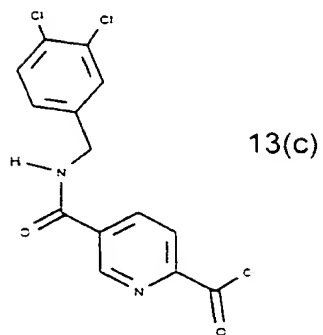
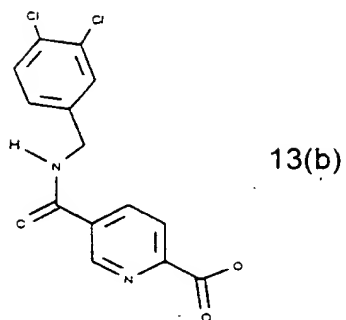
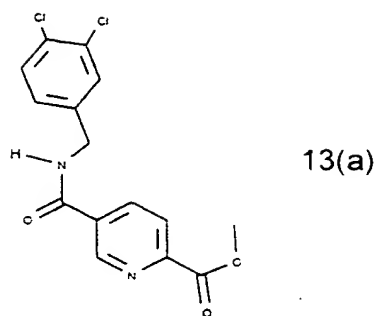
- 120 -

## SCHEME 12 (Cont'd)

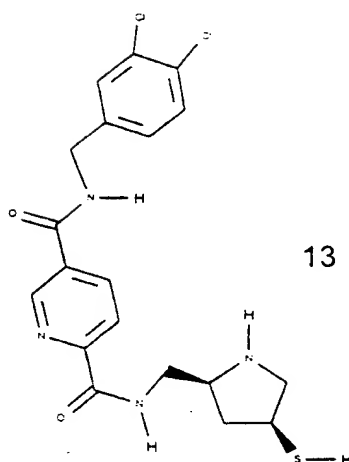
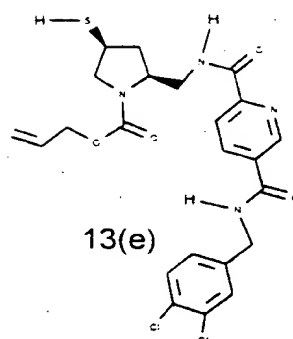
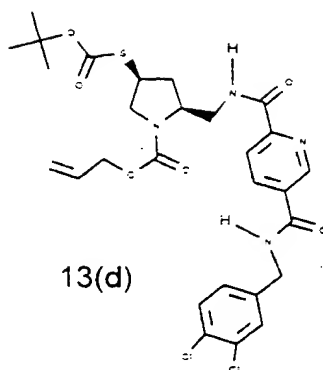


- 121 -

## SCHEME 13

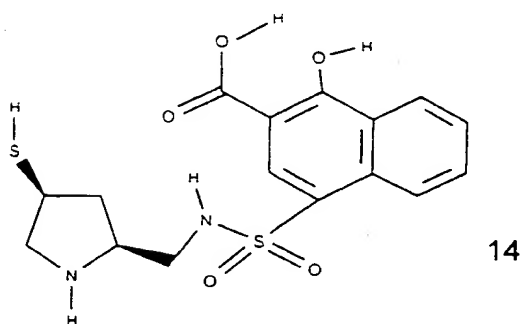
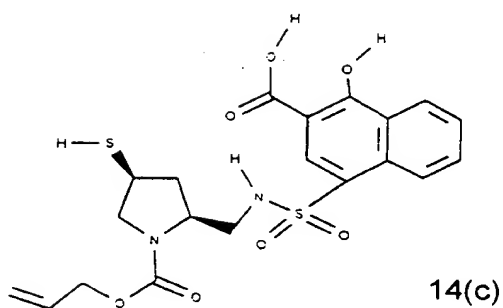
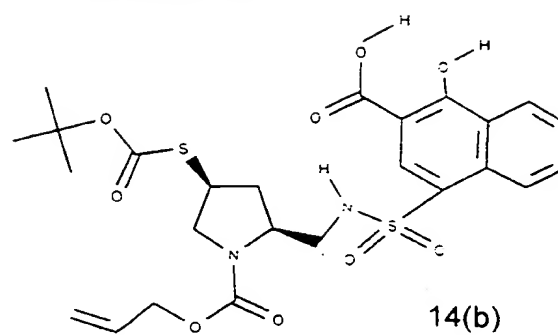
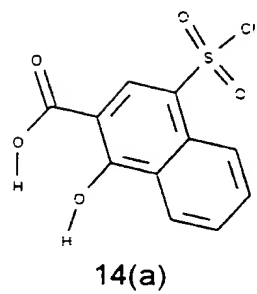


- 122 -



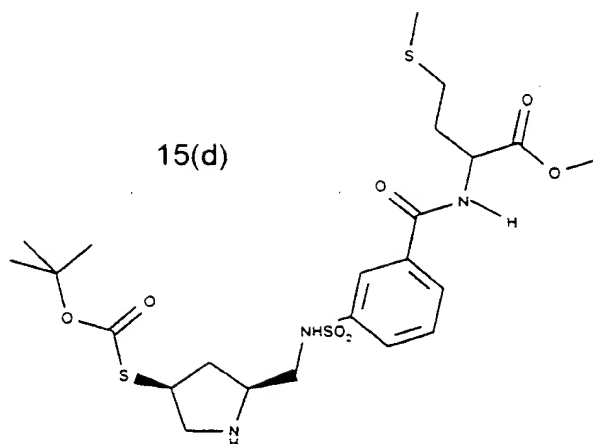
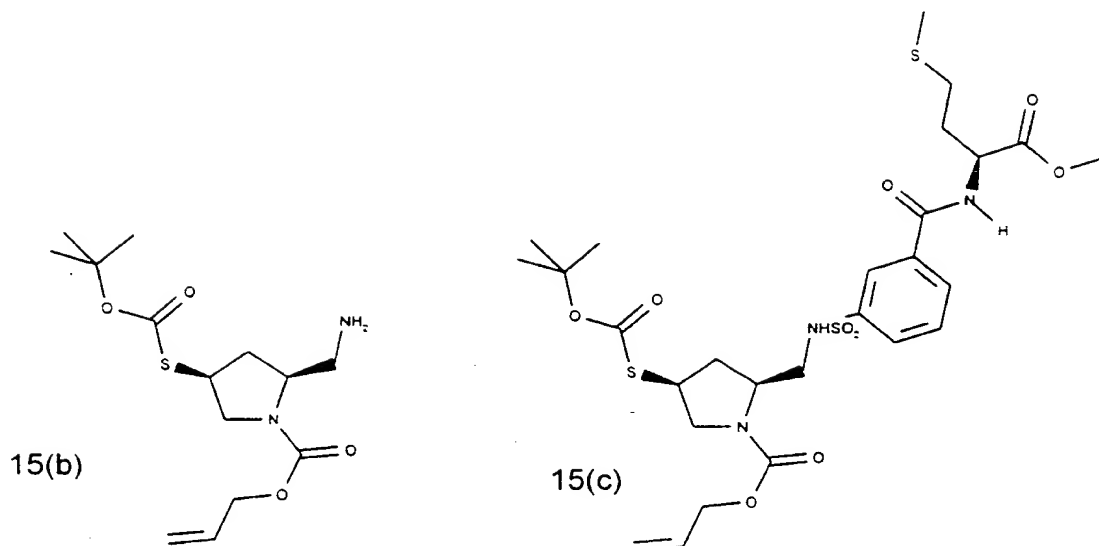
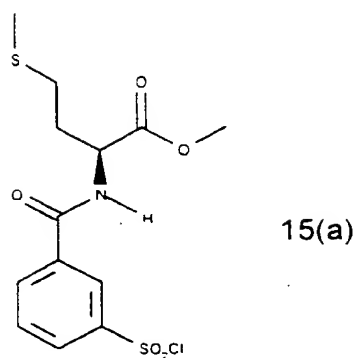
SUBSTITUTE SHEET (RULE 26)

## SCHEME 14



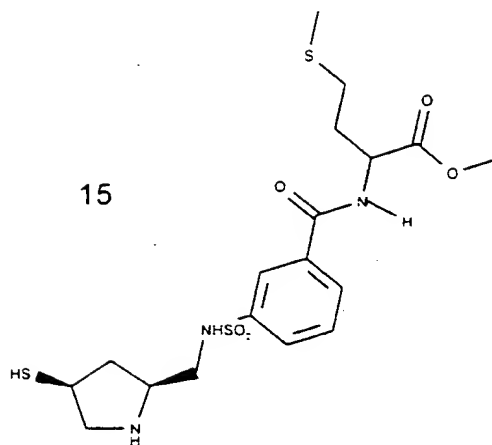
- 124 -

## SCHEME 15

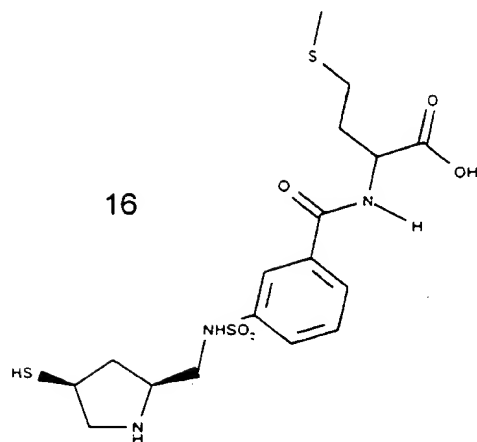


SUBSTITUTE SHEET (RULE 26)

- 125 -



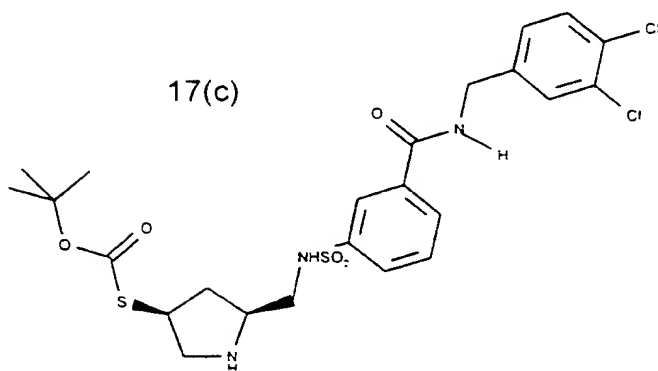
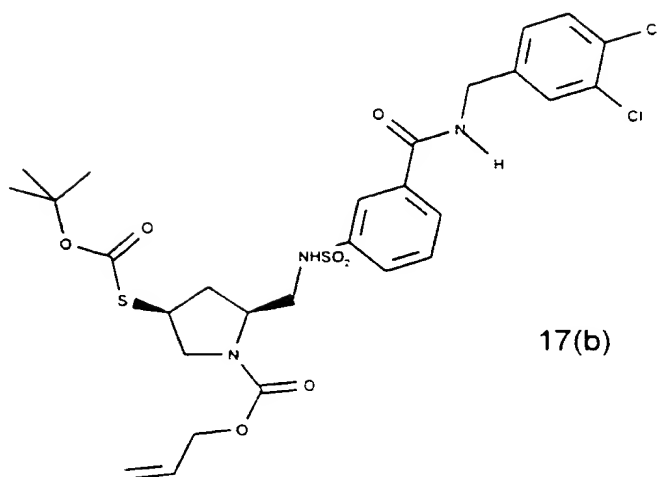
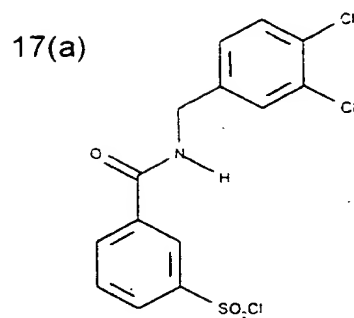
## SCHEME 16





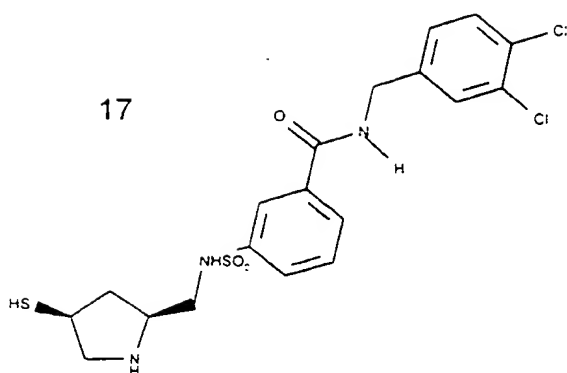
- 127 -

## SCHEME 17

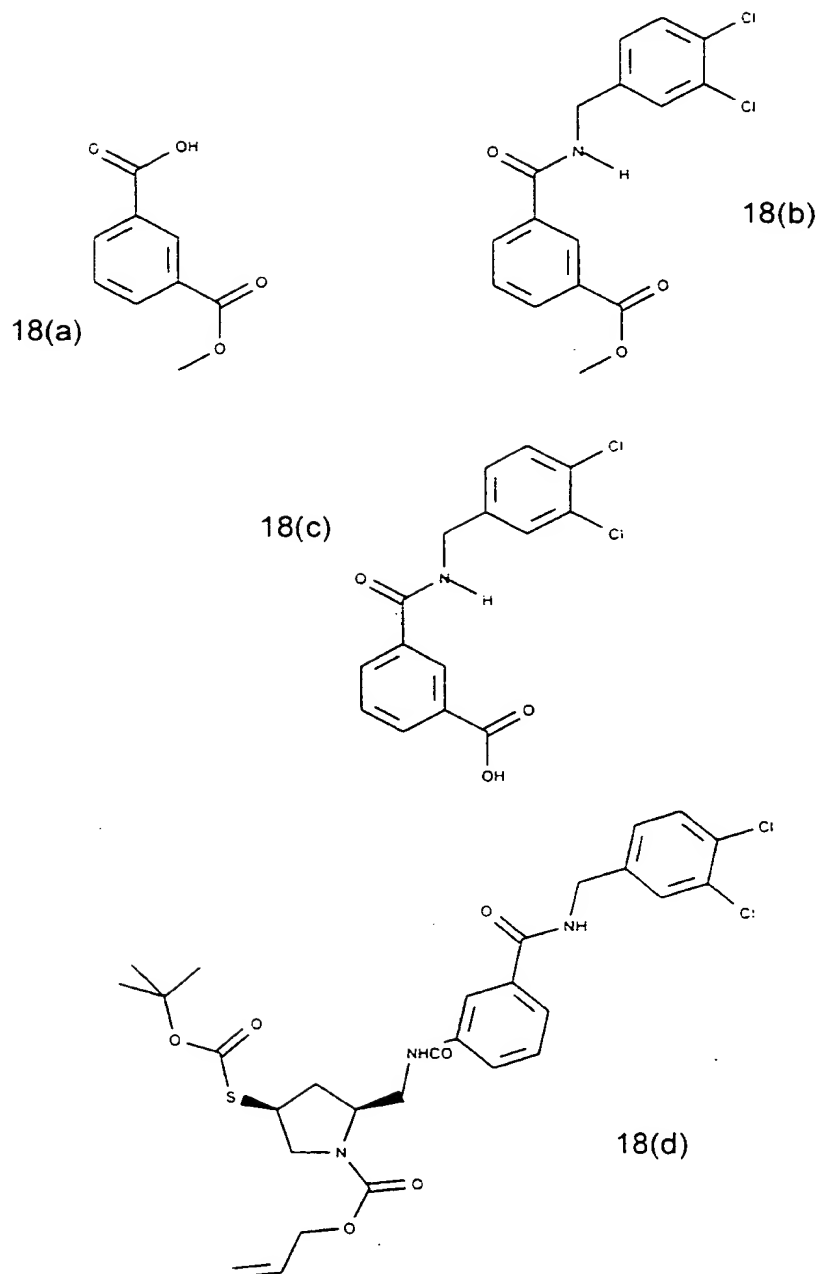


SUBSTITUTE SHEET (RULE 26)

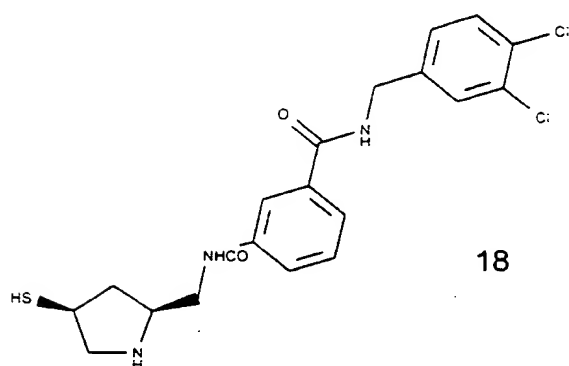
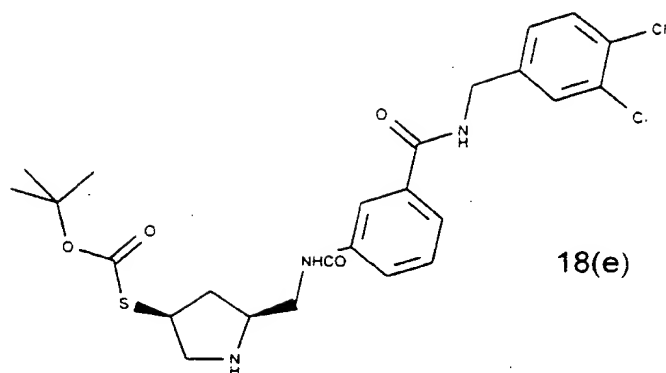
- 128 -



## SCHEME 18

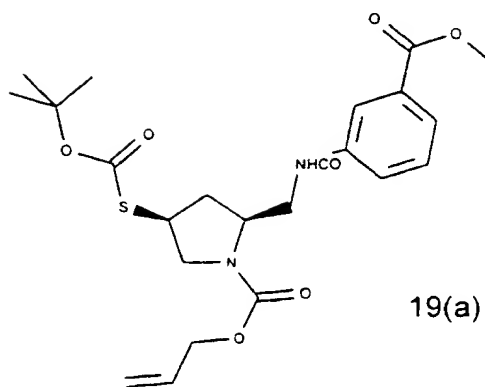


- 130 -

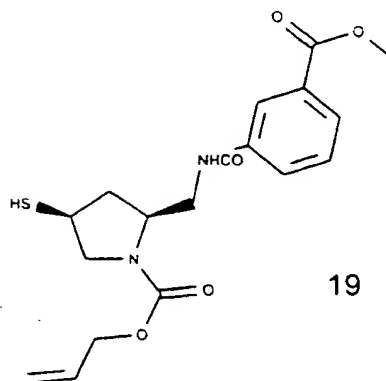


- 131 -

## SCHEME 19



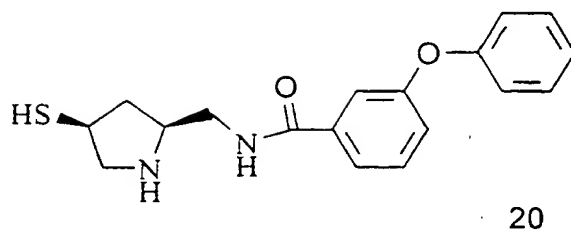
19(a)



19

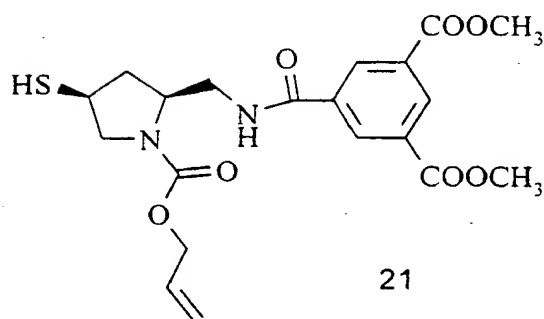
- 132 -

SCHEME 20



20

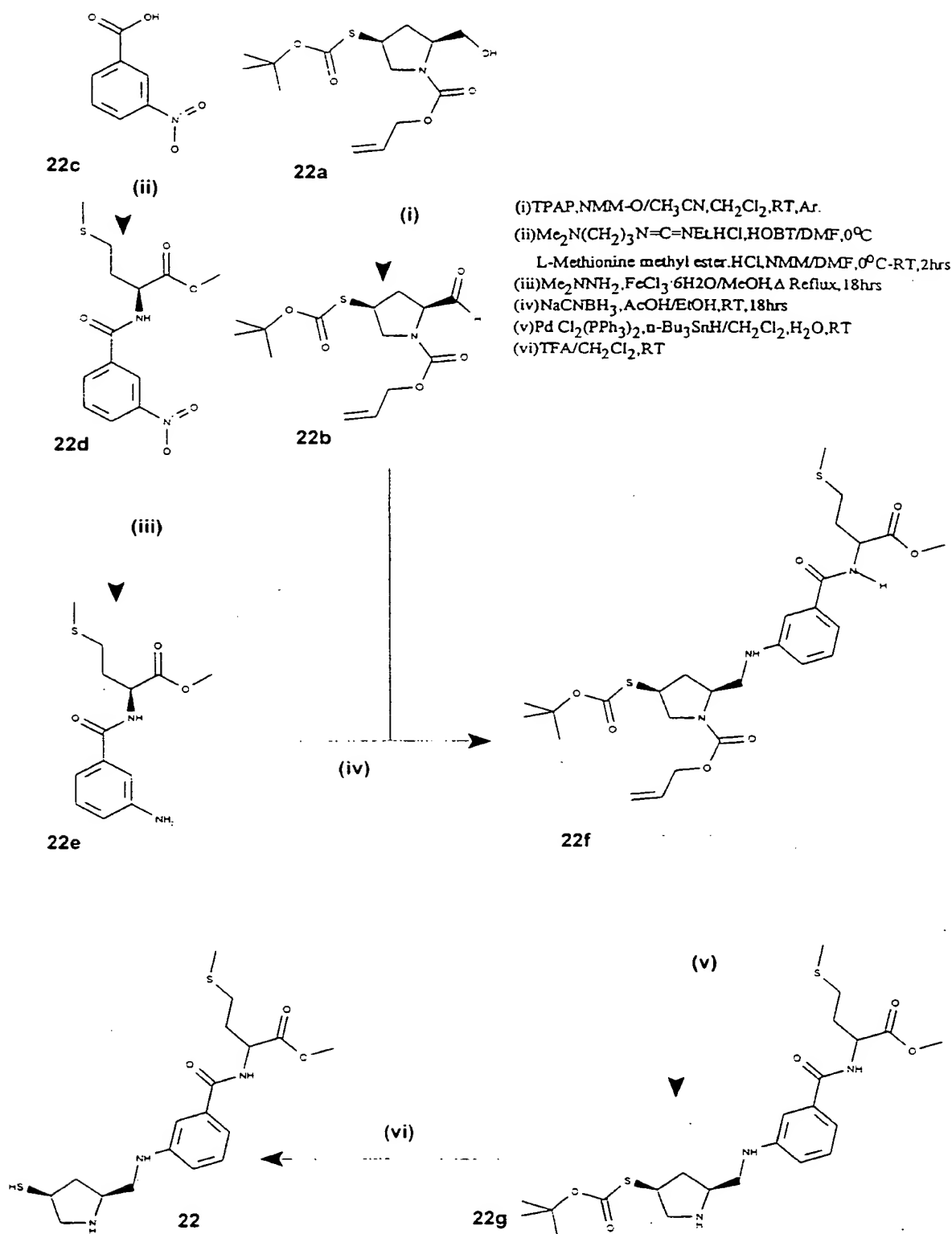
SCHEME 21



21

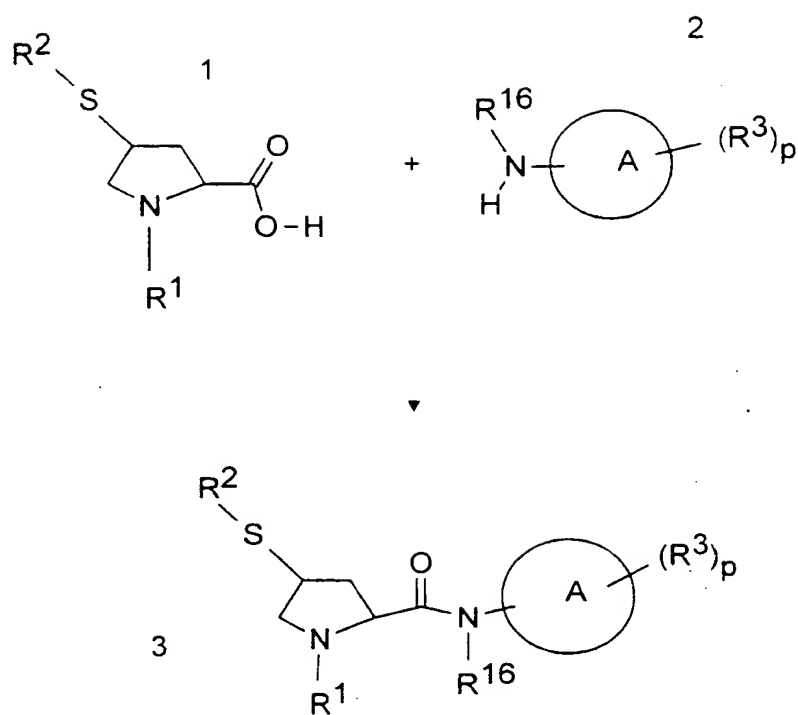
- 133 -

## SCHEME 22



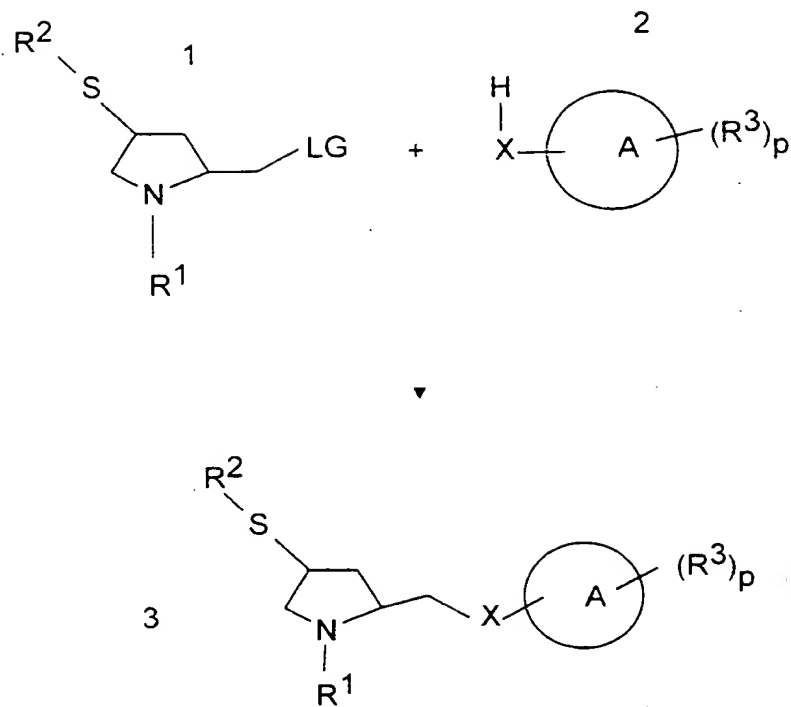
SUBSTITUTE SHEET (RULE 26)

## Scheme 23

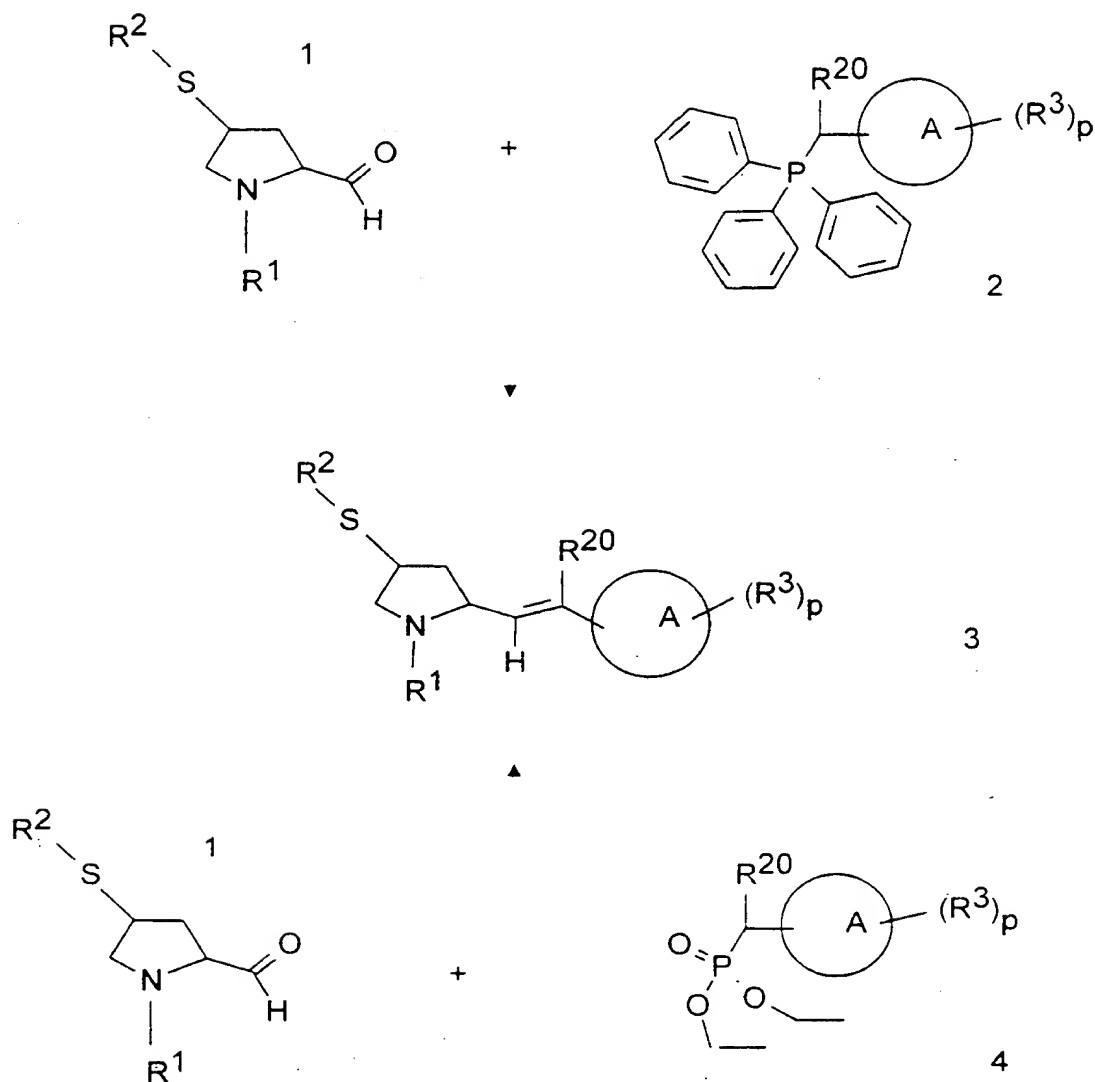




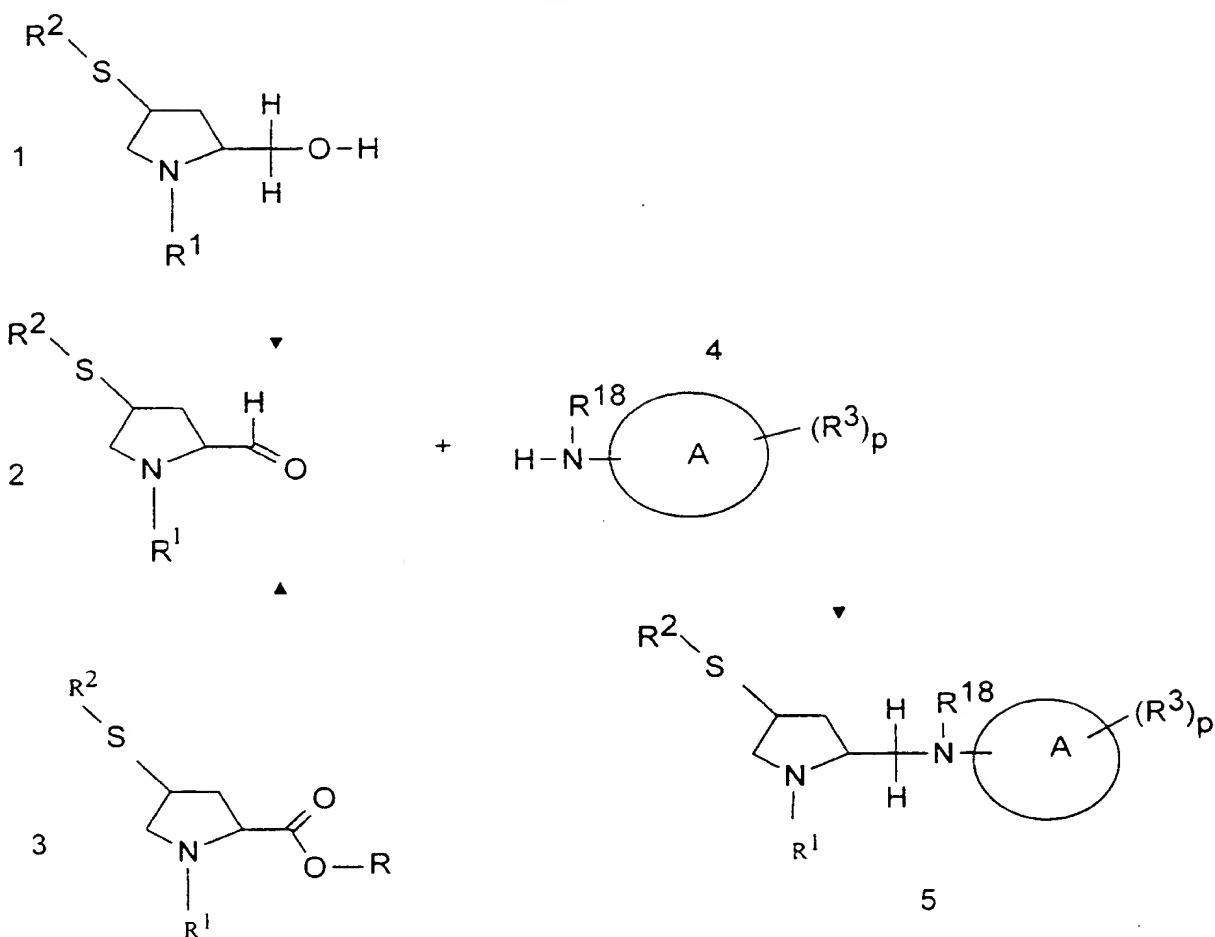
## Scheme 24



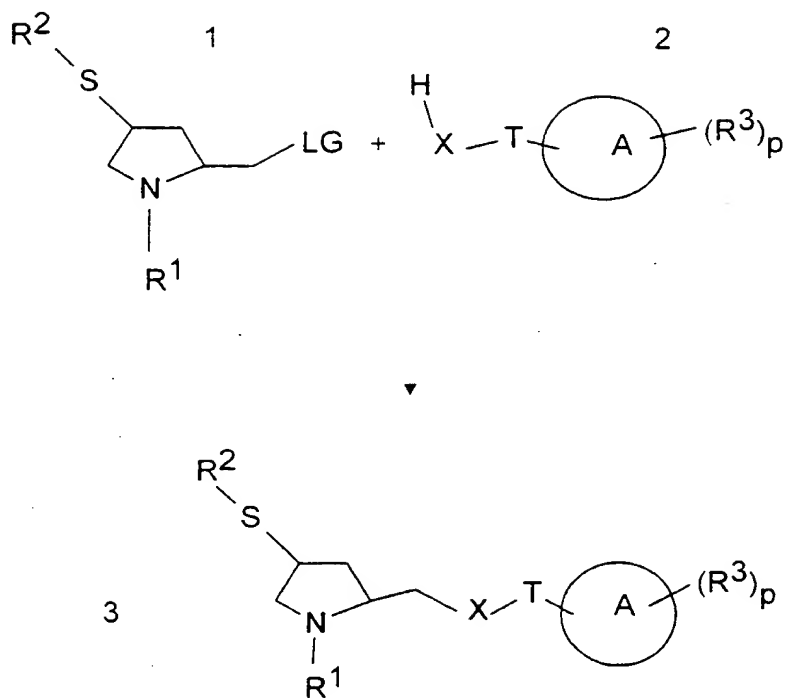
## Scheme 25



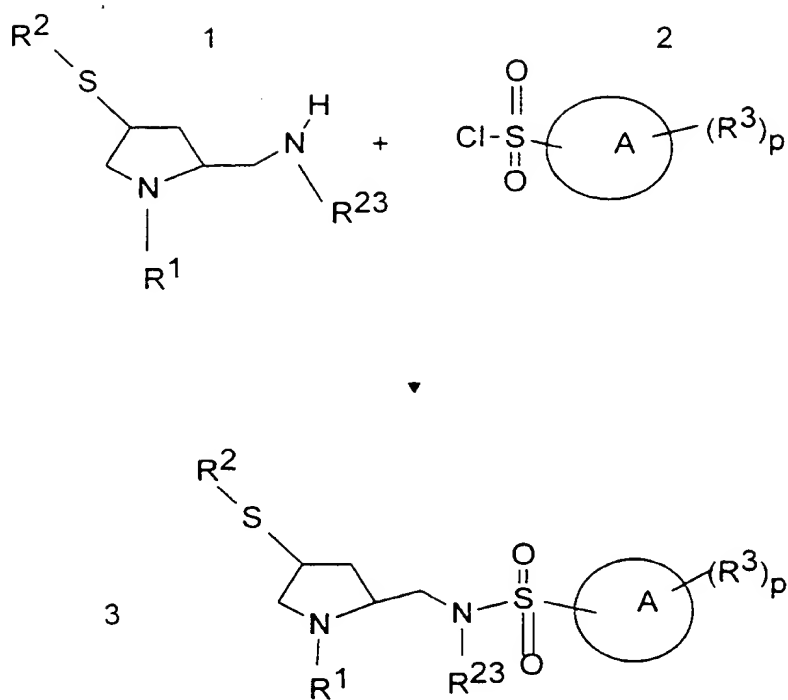
## Scheme 26



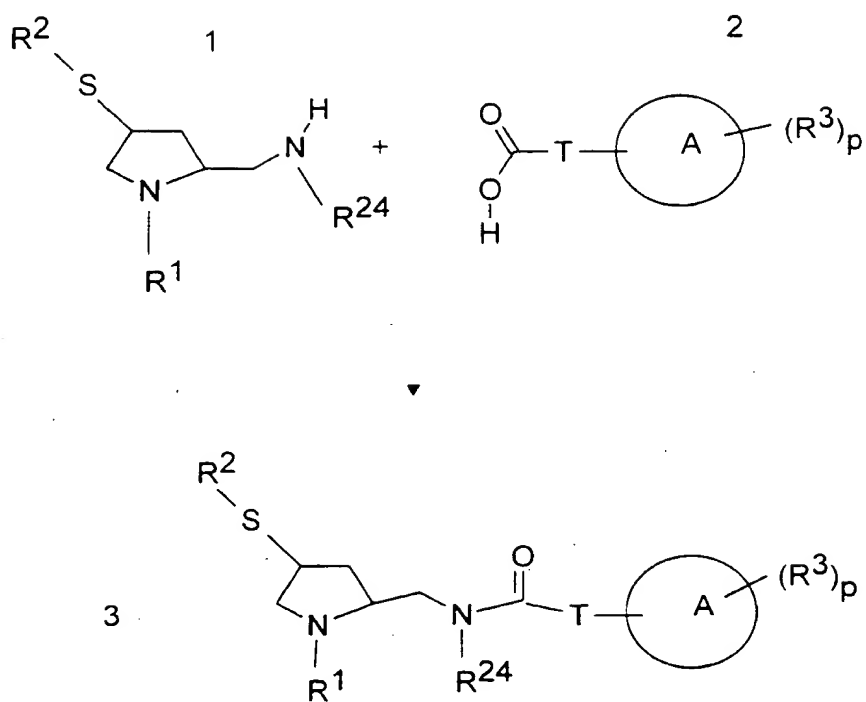
## Scheme 27



## Scheme 28

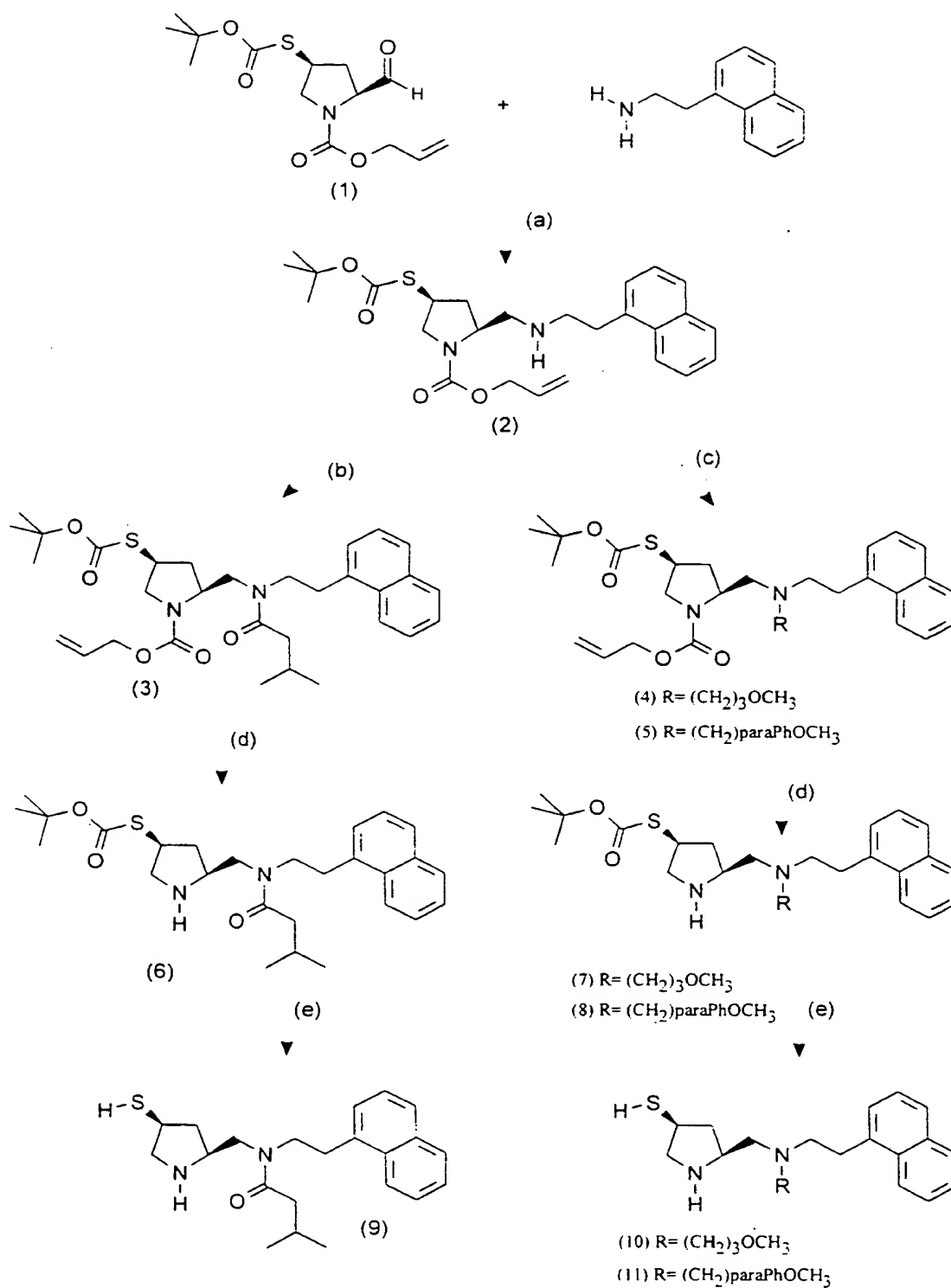


## Scheme 29



- 141 -

## Scheme 30



SUBSTITUTE SHEET (RULE 26)

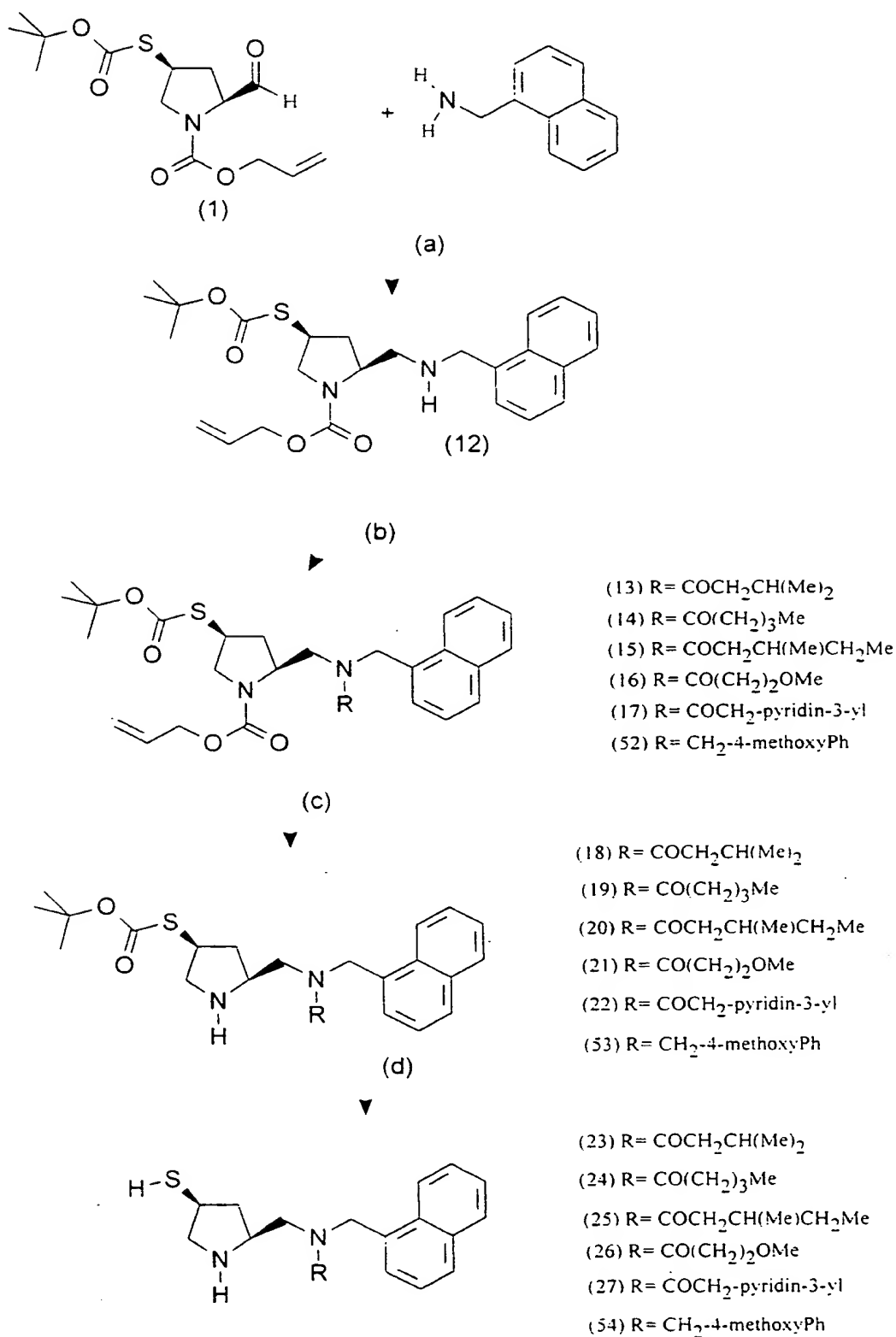
- 142 -

- (a) 4A Molecular sieve/sodium triacetoxo borohydride/dichloromethane/-20deg.
- (b) Isovaleryl chloride/triethylamine/dichloromethane/R.T.
- (c)  $R=(CH_2)_3OCH_3$ , 4A Molecular sieve/sodium triacetoxo borohydride/dichloromethane
- (c)  $R=CH_2paraPhOCH_3$ , paraMethoxybenzyl chloride/sodium bicarbonate/ $H_2O$ /dichloromethane
- (d) Tributyltin hydride/bis(triphenylphosphine)palladium(0) chloride/dichloromethane
- (e) Trifluoroacetic acid/R.T..



- 143 -

## Scheme 31



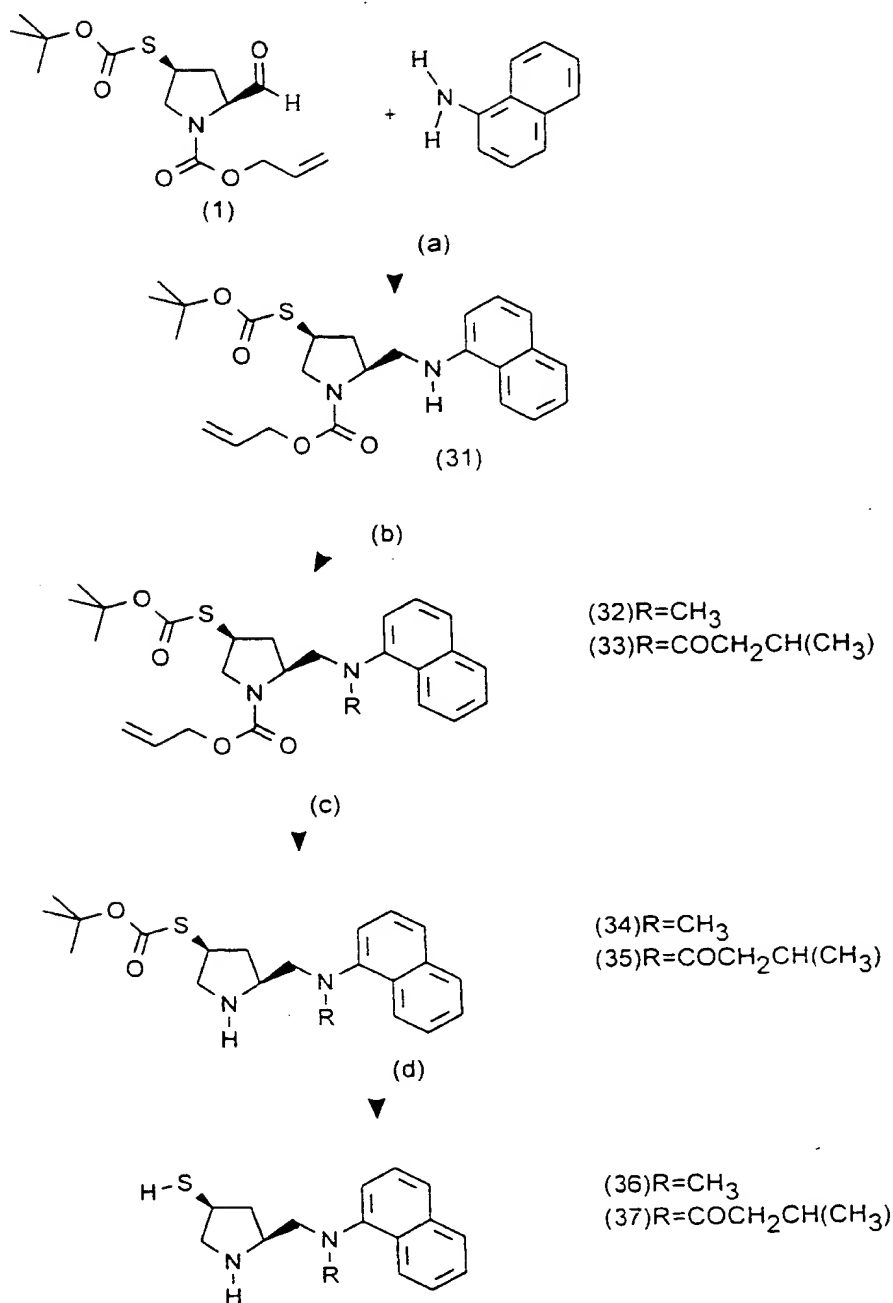
SUBSTITUTE SHEET (RULE 26)

- 144 -

- (a) 4A Molecular sieve/sodium triacetoxo borohydride/dichloromethane/-20deg.
- (b) R=13. Isovaleryl chloride/triethylamine/dichloromethane/R.T.  
R=14. Valeryl chloride/triethylamine/dichloromethane/R.T.  
R=15. 3-Methylvaleric acid/EDC/  
/4--Dimethylamino- pyridine/dichloromethane  
R=16. 3-Methoxypropionic acid/EDC  
/4-Dimethylamino-pyridine/dichloromethane  
R=17. 3-Pyridylacetic acid HCl/EDC  
/4-Dimethylamino-pyridine/dichloromethane  
R=52. p-Methoxybenzyl chloride/potassium carbonate/DMF/70degs.
- (c) Tributyltin hydride/bis(triphenylphosphine)palladium(0) chloride/dichloromethane.
- (d) Trifluoroacetic acid/R.T.

- 145 -

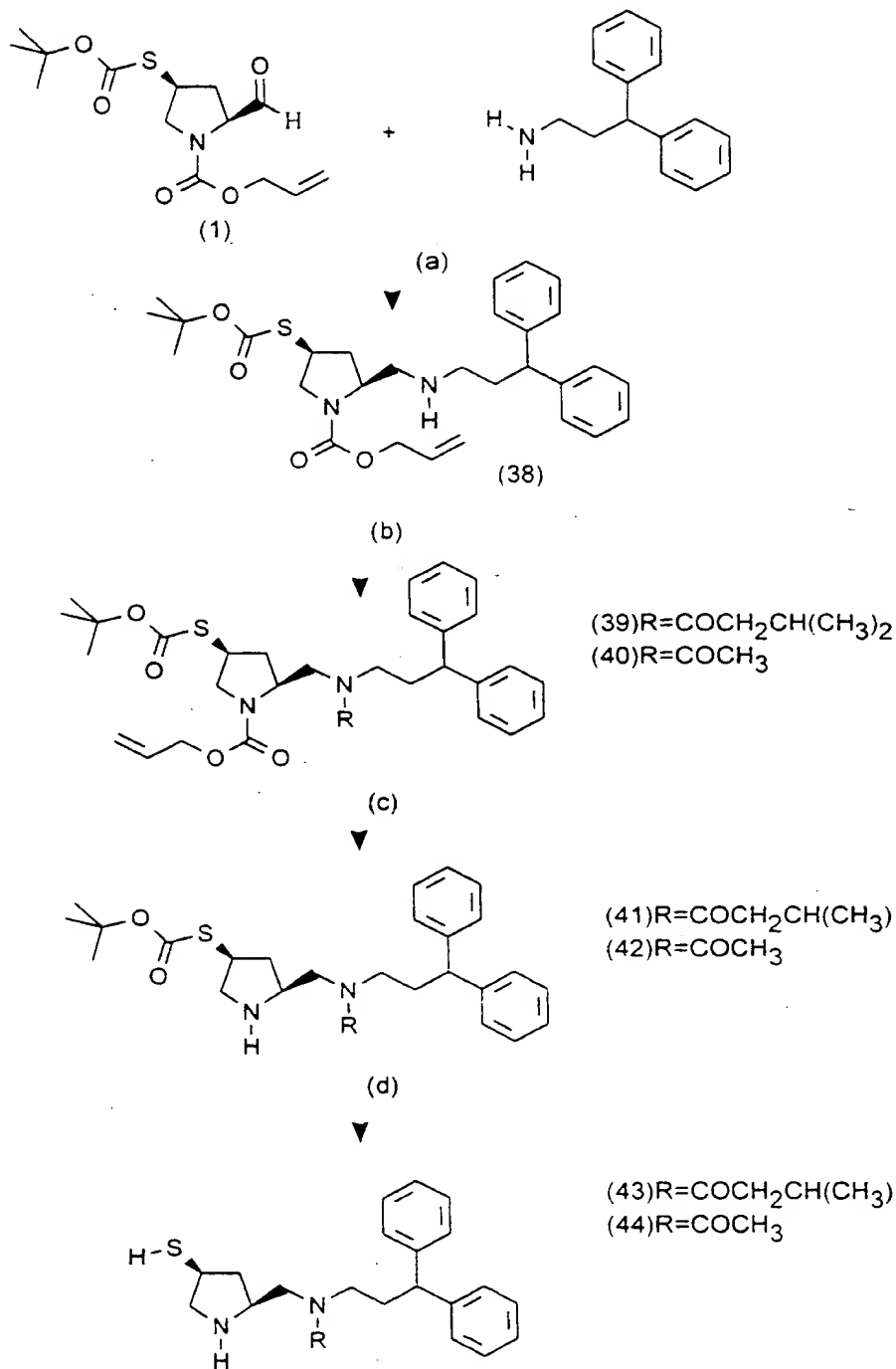
## Scheme 32



- (a) 3A Molecular sieve/acetic acid/ethanol/sodium cyanoboro hydride/R.T.  
 (b) R=CH<sub>3</sub>, Methyl iodide/dimethyl formamide/potassium carbonate/80 deg.  
 R=COCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, Isovaleryl chloride/triethylamine/dichloromethane/R.T.  
 (c) Tributyltin hydride/bis(triphenylphosphine)palladium(0)chloride/dichloromethane  
 (d) Trifluoroacetic acid/R.T.

SUBSTITUTE SHEET (RULE 26)

## Scheme 33



(a) 4A Molecular sieve/sodium triacetoxy borohydride/dichloromethane/-20deg.

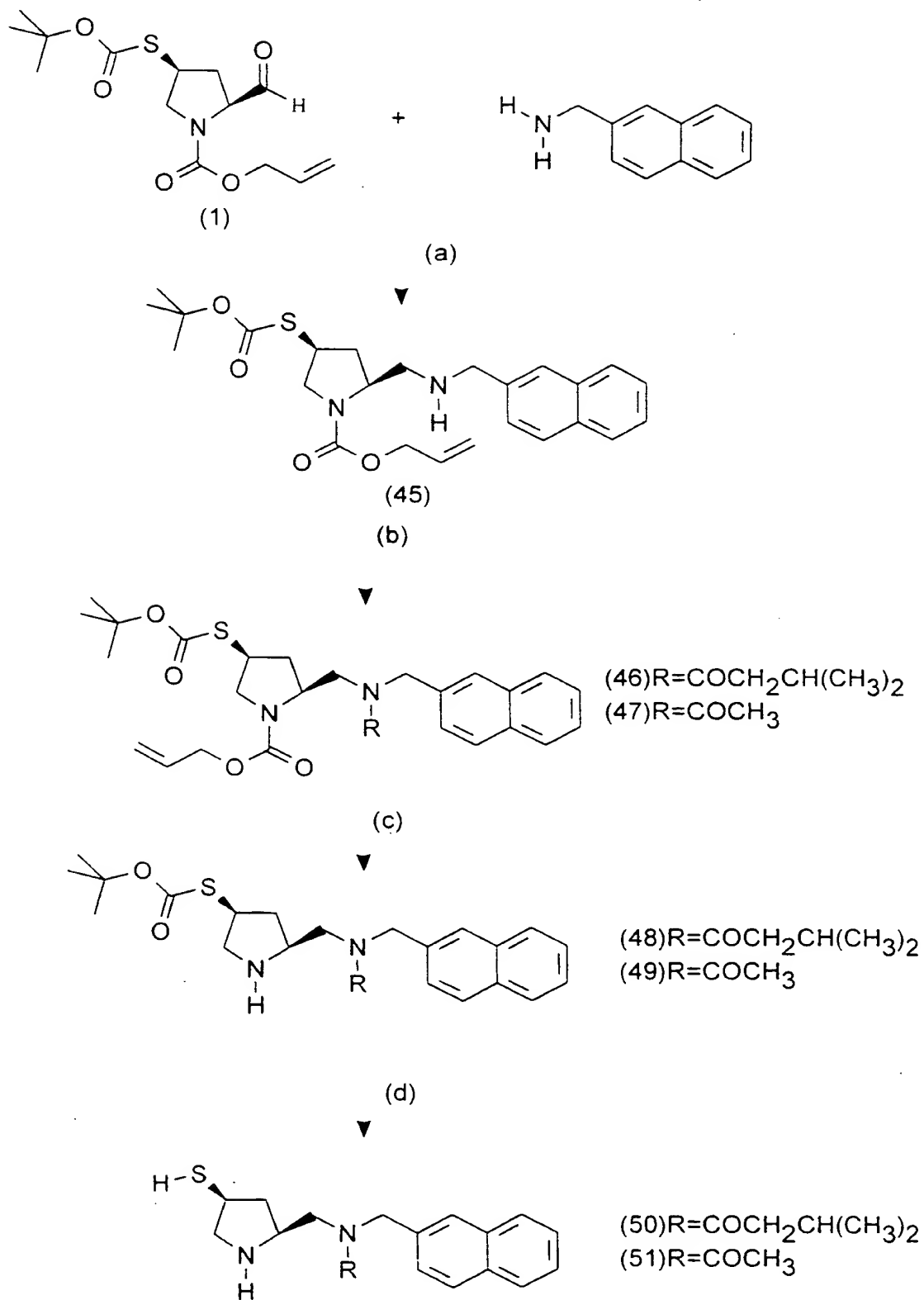
(b) R=COCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, Isovaleryl chloride/triethylamine/dichloromethane/R.T.  
R=COCH<sub>3</sub>, Acetyl chloride/dichloromethane/triethylamine/R.T.

(c) Tributyltin hydride/bis(triphenylphosphine)palladium(0) chloride/dichloromethane

**SUBSTITUTE SHEET (RULE 26)**

- 147 -

## Scheme34



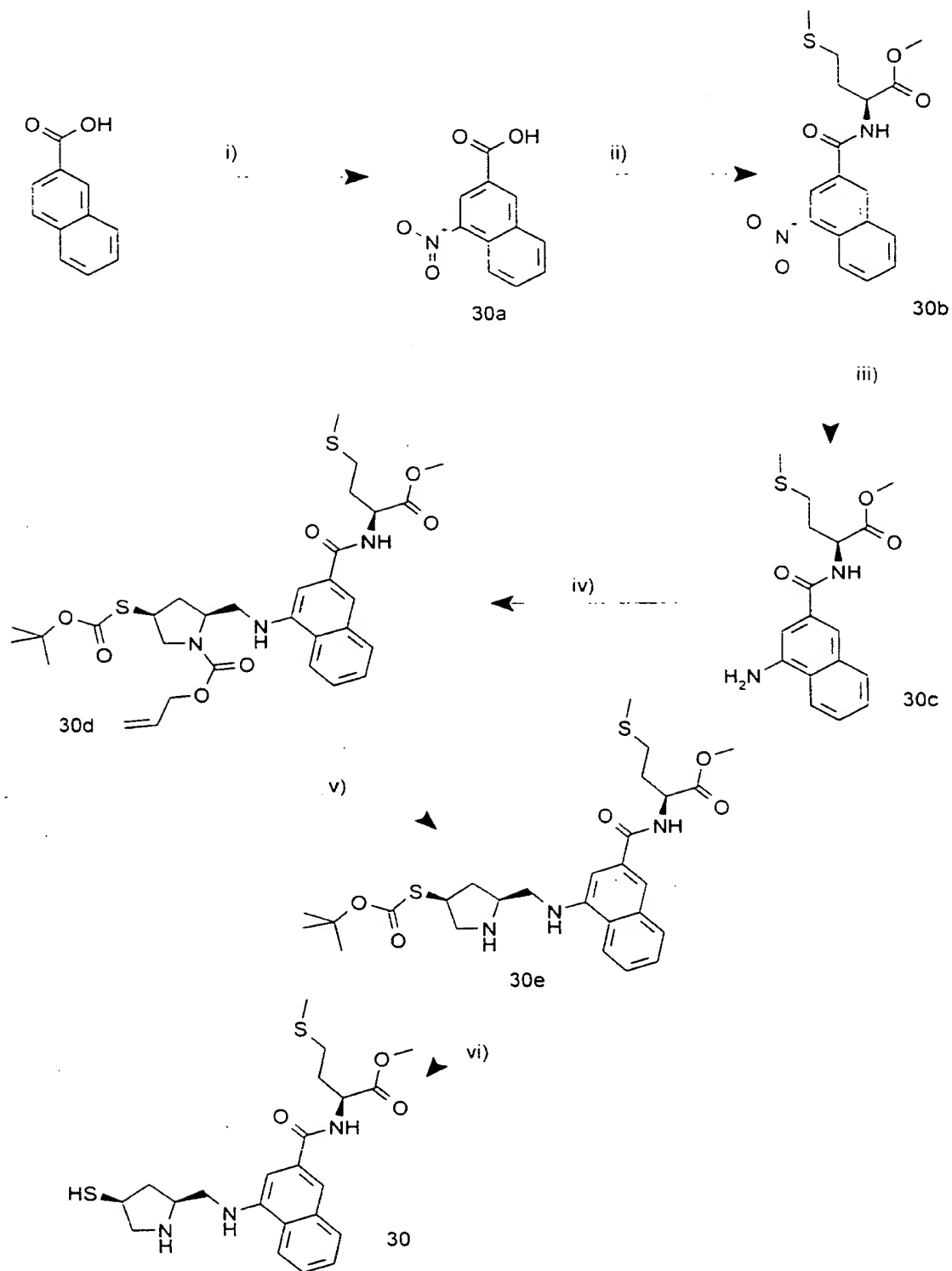
SUBSTITUTE SHEET (RULE 26)

- 148 -

- (a) 4A Molecular sieve/sodium triacetoxy borohydride/dichloromethane/-20deg.
- (b)  $R = \text{COCH}_2\text{CH}(\text{CH}_3)_2$ , Isovaleryl chloride/triethylamine/dichloromethane/R.T.  
 $R = \text{COCH}_3$ , Acetyl chloride/dichloromethane/triethylamine/R.T.
- (c) Tributyltin hydride/bis(triphenylphosphine)palladium(0) chloride/dichloromethane
- (d) Trifluoroacetic acid/R.T.

- 149 -

## Scheme 35



SUBSTITUTE SHEET (RULE 26)

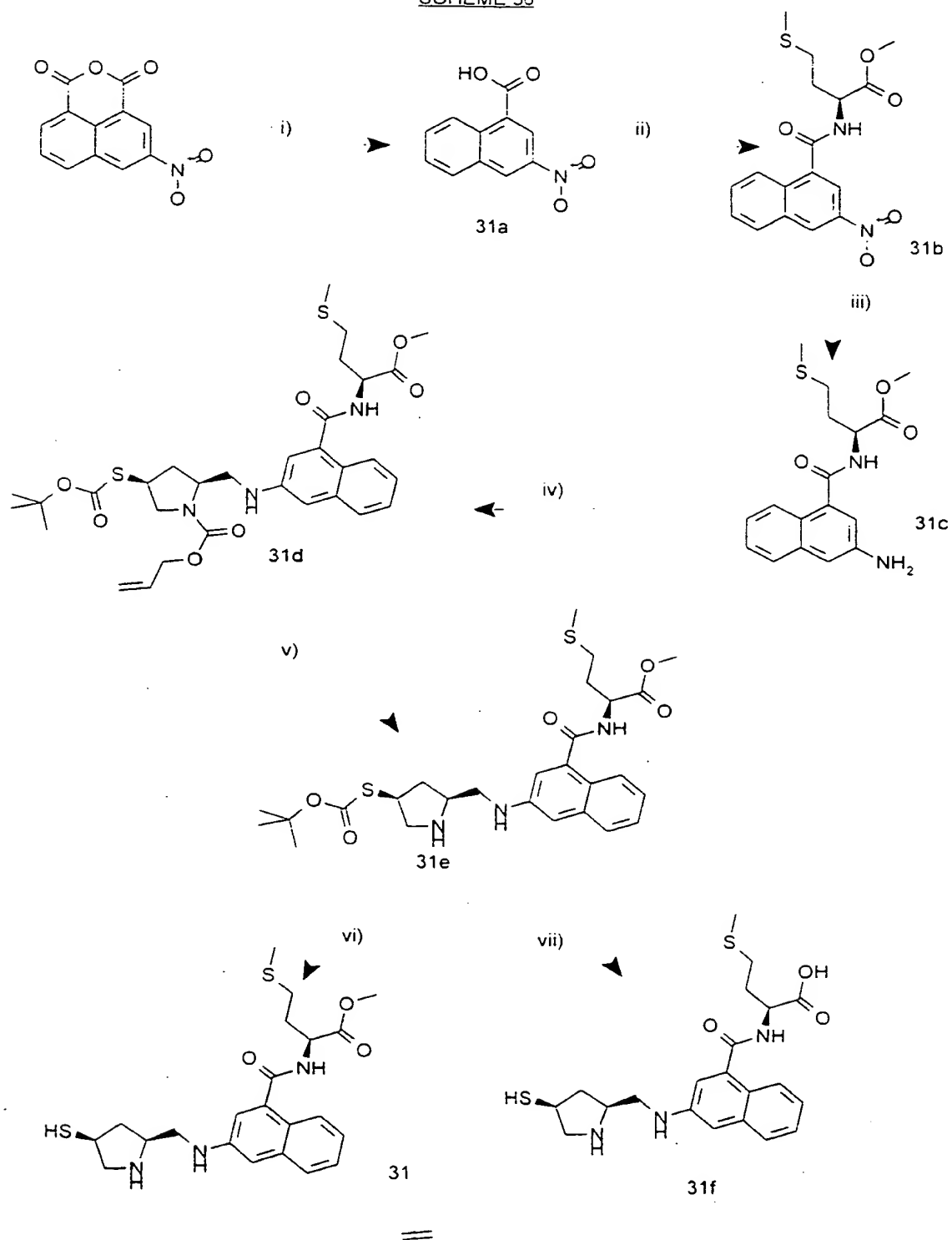
- 150 -

- i)  $\text{HNO}_3$ ,  $50^\circ\text{C}$
- ii)  $(\text{COCl})_2$ .DMF/ $\text{CH}_2\text{Cl}_2$   
Et<sub>3</sub>N, L-Methionine methyl ester hydrochloride
- iii)  $\text{Me}_2\text{NNH}_2$ . $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ /MeOH  $\Delta$  Reflux
- iv) **22b**/MeOH.3A<sup>o</sup> sieves  
AcOH.NaCNBH<sub>3</sub>
- v)  $\text{PdCl}_2(\text{PPh}_3)_2$ , <sup>n</sup>Bu<sub>3</sub>SnH/ $\text{CH}_2\text{Cl}_2$ , H<sub>2</sub>O
- vi) TFA



- 151 -

## SCHEME 36



SUBSTITUTE SHEET (RULE 26)

- 152 -

i) G.J. Leuck et al JACS 51, 1831, 1929

ii) EDC.HOBT/DMF 0°C

NMM.L-Methionine methyl ester hydrochloride 0°C-RT

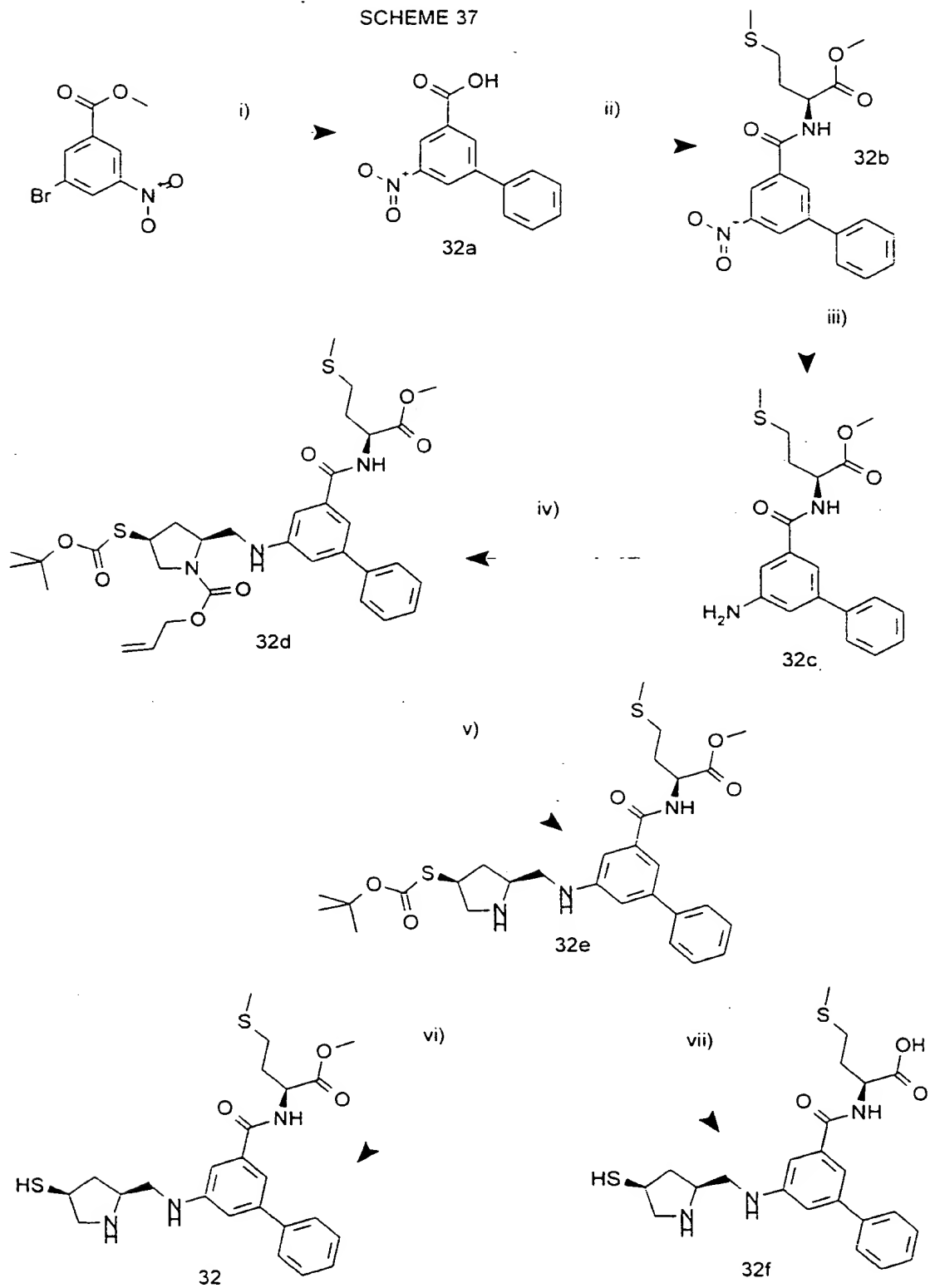
iii)  $\text{Me}_2\text{NNH}_2$ . $\text{FeCl}_3$  6 $\text{H}_2\text{O}$ /MeOH  $\Delta$  Refluxiv) **22b**/MeOH.3A° sievesAcOH.NaCNBH<sub>3</sub>v)  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $^n\text{Bu}_3\text{SnH}$ /CH<sub>2</sub>Cl<sub>2</sub>.H<sub>2</sub>O

vi) TFA

vii) 2N NaOH/MeOH

- 153 -

SCHEME 37



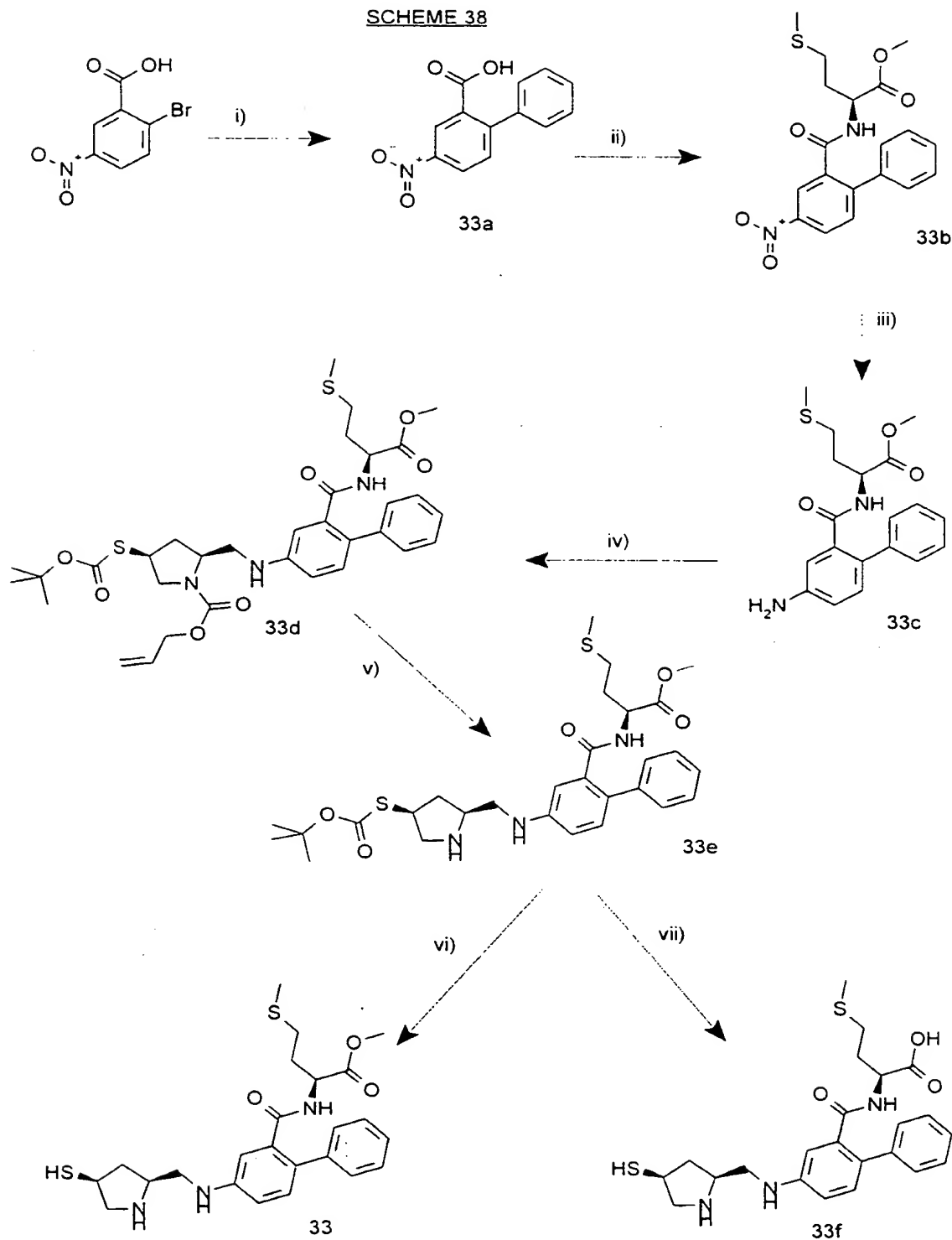
SUBSTITUTE SHEET (RULE 26)

- 154 -

- i)  $\text{PhB(OH)}_2$ ,  $(\text{PPh}_3)_4 \text{Pd}^0$  /DME. $\text{NaHCO}_3$ (aq)  $\Delta$  Reflux
- ii) EDC.HOBT/DMF  $0^\circ\text{C}$   
NMM.L-Methionine methyl ester hydrochloride  $0^\circ\text{C}$ -RT
- iii)  $\text{Me}_2\text{NNH}_2$ . $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ /MeOH  $\Delta$  Reflux
- iv) **22b**/MeOH.3A $^\circ$  sieves  
AcOH. $\text{NaCNBH}_3$
- v)  $\text{PdCl}_2(\text{PPh}_3)_2$ . $^n\text{Bu}_3\text{SnH}$ / $\text{CH}_2\text{Cl}_2$ . $\text{H}_2\text{O}$
- vi) TFA
- vii) 2N NaOH/MeOH

- 155 -

SCHEME 38

i)  $\text{PhB(OH)}_2$ ,  $(\text{PPh}_3)_4 \text{Pd}^0$  /DME,  $\text{NaHCO}_3(\text{aq})$   $\Delta$  Refluxii) EDC, HOBT/DMF  $0^\circ\text{C}$ NMM, L-Methionine methyl ester hydrochloride  $0^\circ\text{C}$ -RTiii)  $\text{Me}_2\text{NNH}_2$ ,  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  /MeOH  $\Delta$  Refluxiv) **22b**/MeOH,  $3\text{\AA}$  sieves

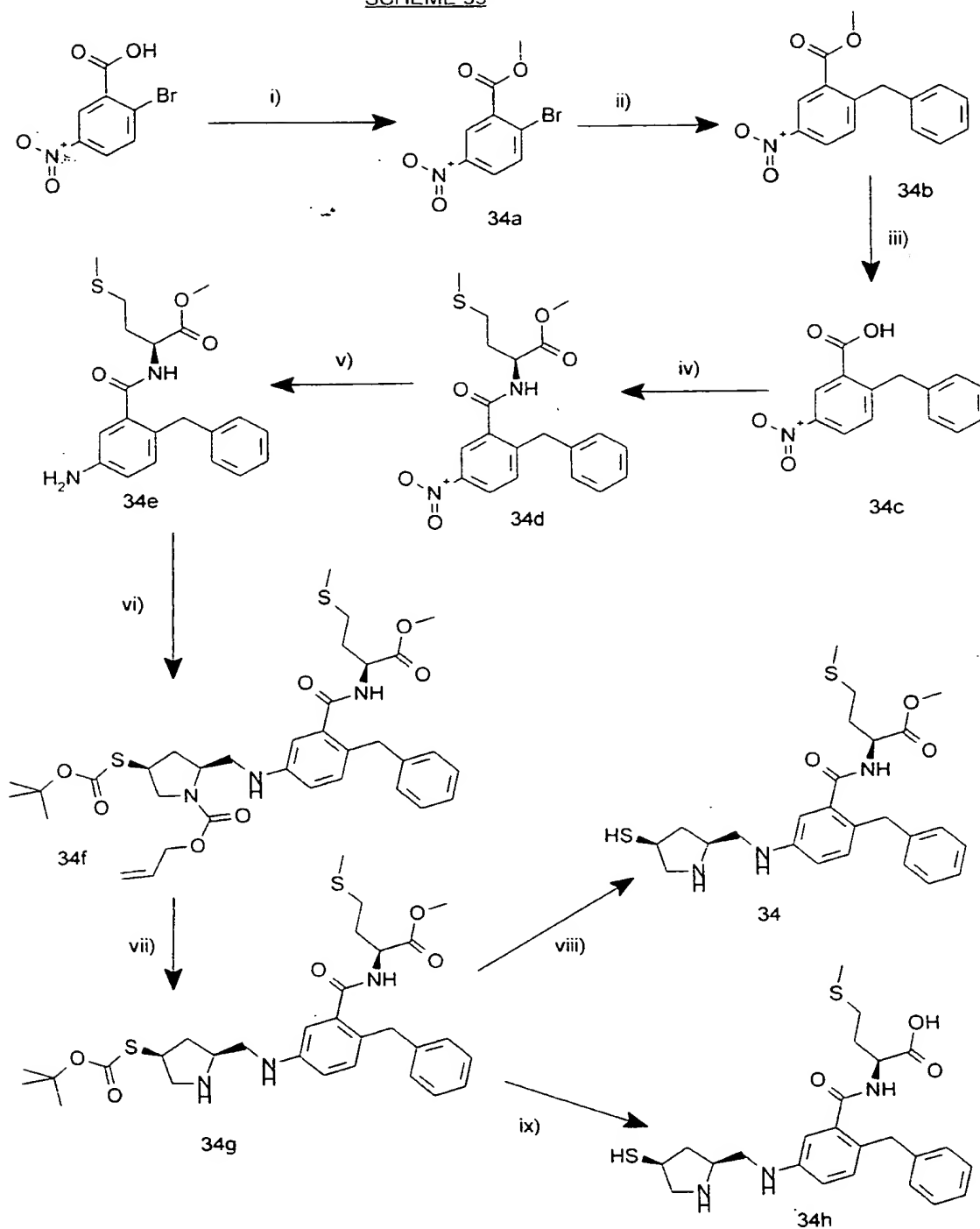
SUBSTITUTE SHEET (RULE 26)

- 156 -

AcOH.NaCNBH<sub>3</sub>  
v) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, <sup>n</sup>Bu<sub>3</sub>SnH/CH<sub>2</sub>Cl<sub>2</sub>.H<sub>2</sub>O  
vi) TFA  
vii) 2N NaOH/MeOH

- 157 -

SCHEME 39

i)  $\text{SO}_2\text{Cl}_2/\text{MeOH}$   $\Delta$  Refluxii)  $\text{BzZnBr}$ ,  $\text{PdCl}_2(\text{PPh}_3)_2$  / THFiii) 2N  $\text{NaOH}/\text{MeOH}$ iv) EDC, HOBT/DMF  $0^\circ\text{C}$ NMM, L-Methionine methyl ester hydrochloride  $0^\circ\text{C}$ -RTv)  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}/\text{EtOAc}$   $\Delta$  Reflux

SUBSTITUTE SHEET (RULE 26)

- 158 -

vi) **22b**/MeOH.3A° sievesAcOH.NaCNBH<sub>3</sub>vii) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>.<sup>n</sup>Bu<sub>3</sub>SnH/CH<sub>2</sub>Cl<sub>2</sub>.H<sub>2</sub>O

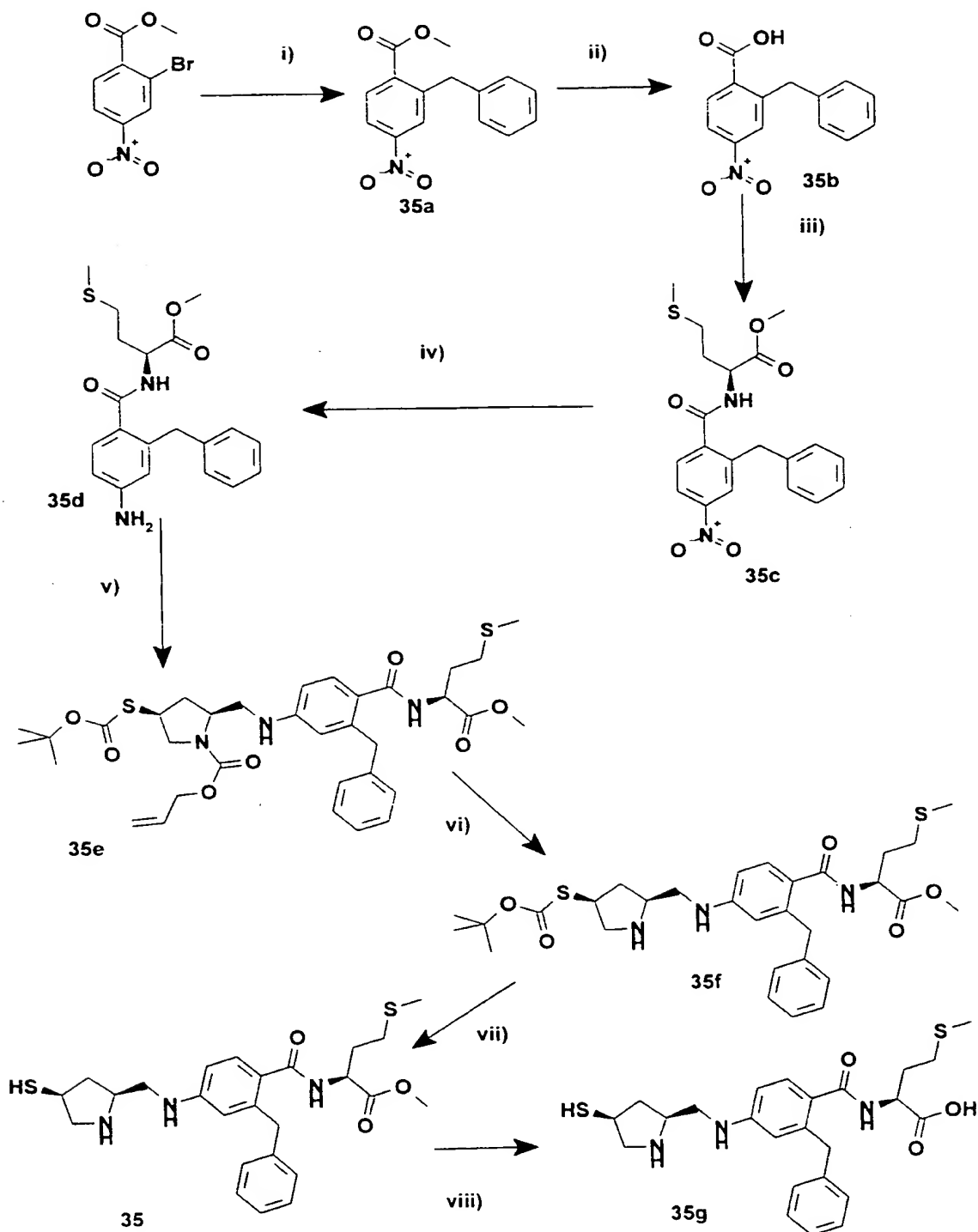
viii) TFA

ix) 2N NaOH/MeOH



- 159 -

SCHEME 40



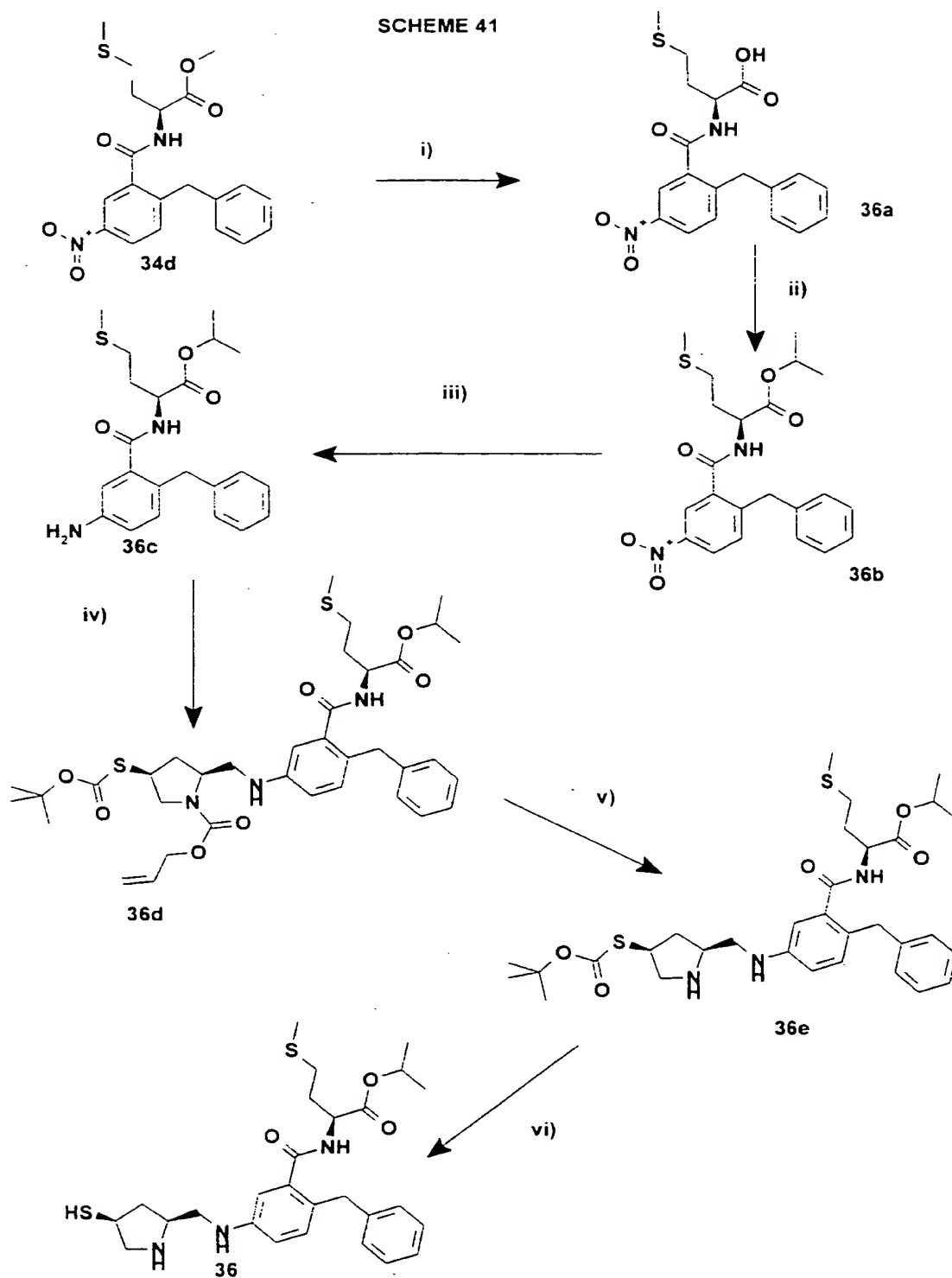
SUBSTITUTE SHEET (RULE 26)

- 160 -

- NMM.L-Methionine methyl ester hydrochloride 0°C-RT
- iv)  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O} / \text{EtOAc}$   $\Delta$  Reflux
  - v) **22b**/MeOH.3A° sieves  
AcOH.NaCNBH<sub>3</sub>
  - vi)  $\text{PdCl}_2(\text{PPh}_3)_2$ , <sup>n</sup>Bu<sub>3</sub>SnH/CH<sub>2</sub>Cl<sub>2</sub>.H<sub>2</sub>O
  - vii) TFA
  - viii) 2N NaOH/MeOH

- 161 -

SCHEME 41



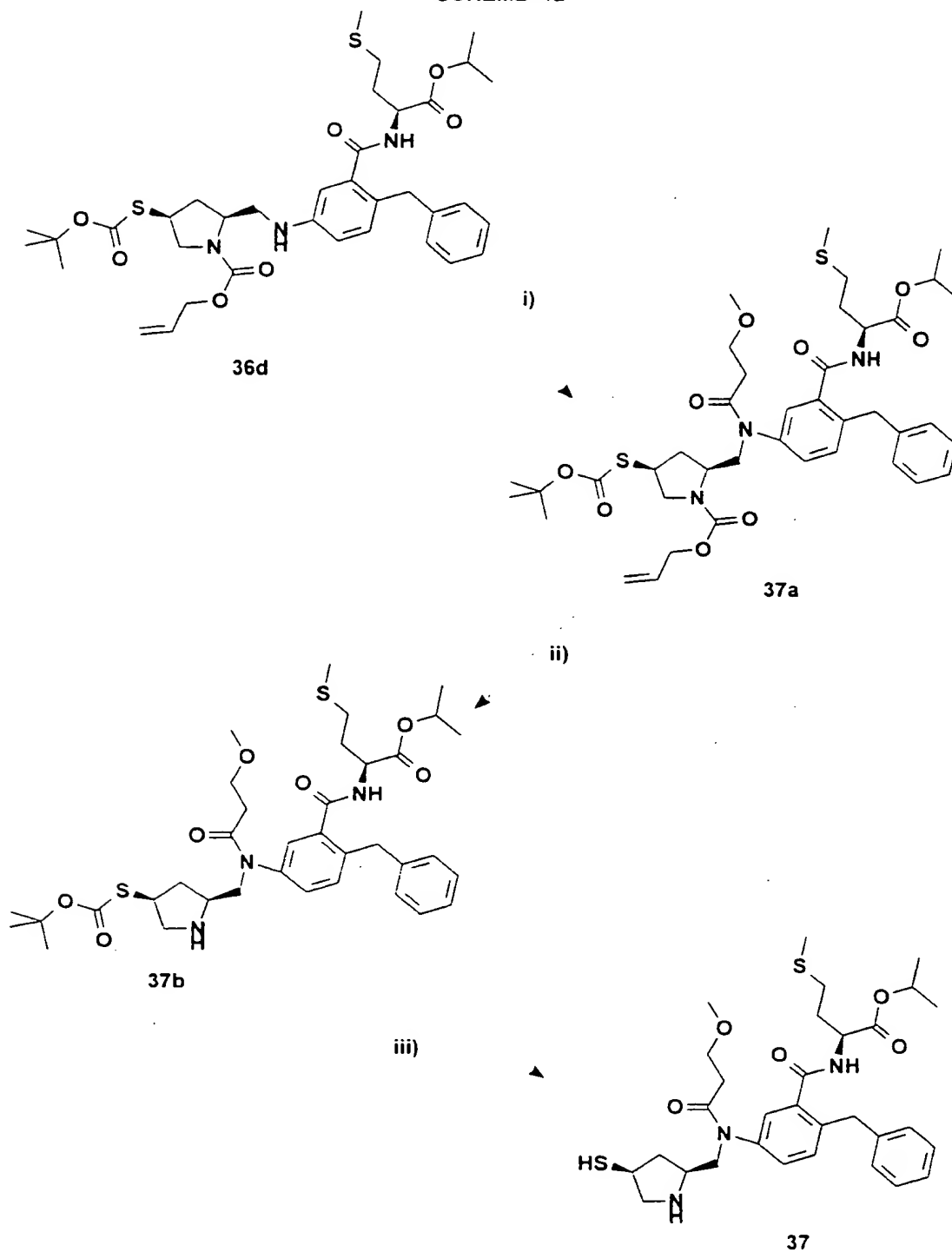
SUBSTITUTE SHEET (RULE 26)

- 162 -

- i) 2N NaOH/MeOH
- ii)  $\text{SO}_2\text{Cl}_2$ /IPA  $\Delta$  Reflux
- iii)  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ /EtOAc  $\Delta$  Reflux
- iv) **22b**/IPA. 3A<sup>o</sup> sieves  
AcOH. NaCNBH<sub>3</sub>
- v)  $\text{PdCl}_2(\text{PPh}_3)_2$ , <sup>n</sup>Bu<sub>3</sub>SnH/CH<sub>2</sub>Cl<sub>2</sub>. H<sub>2</sub>O
- vi) TFA

- 163 -

SCHEME 42

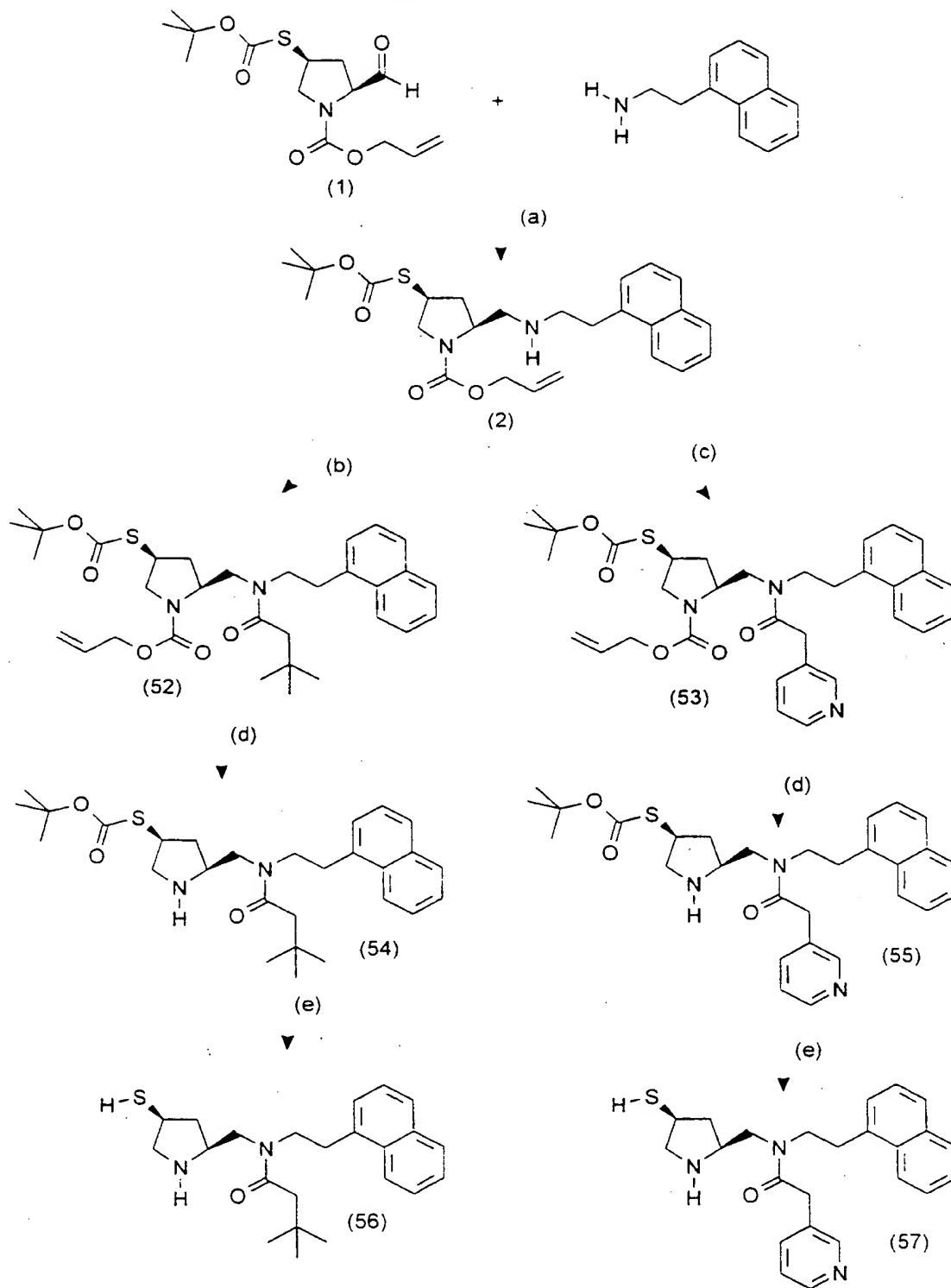


i)  $\text{CH}_3\text{O}(\text{CH}_2)_2\text{CO}_2\text{H.EEDQ}/\text{CH}_2\text{Cl}_2$   
 ii)  $\text{PdCl}_2(\text{PPh}_3)_2, n\text{Bu}_3\text{SnH}/\text{CH}_2\text{Cl}_2.\text{H}_2\text{O}$   
 iii) TFA

SUBSTITUTE SHEET (RULE 26)

- 164 -

Scheme 43



SUBSTITUTE SHEET (RULE 26)

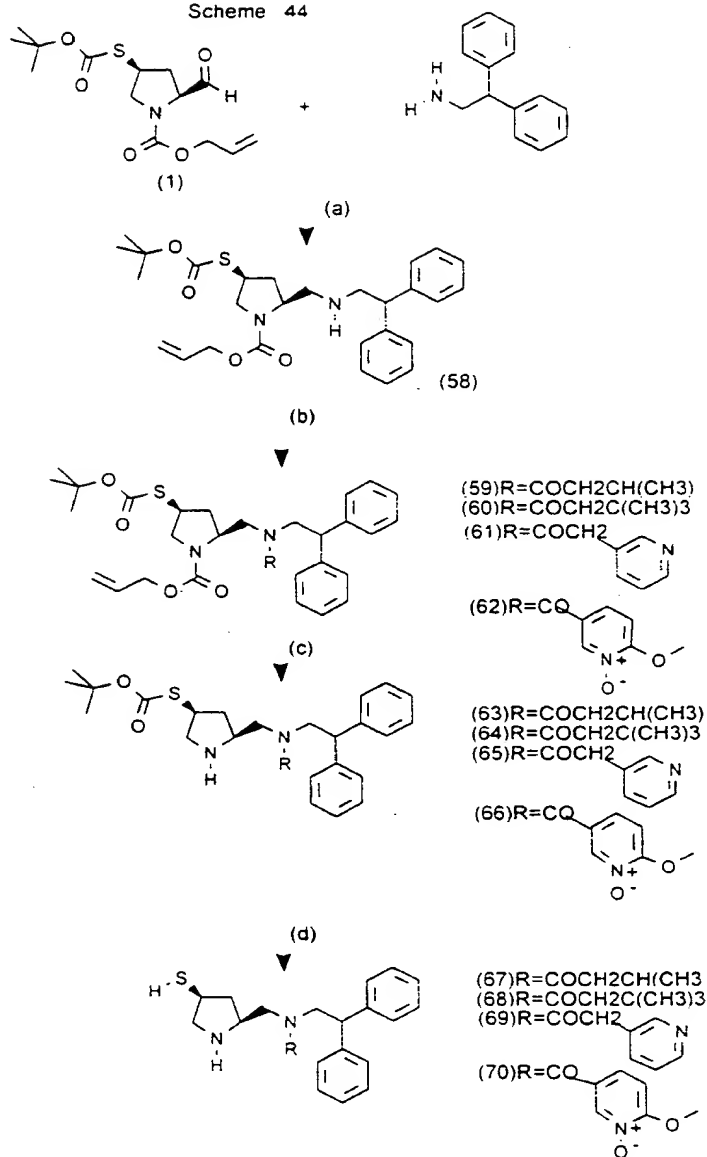
- 165 -

## Scheme 43(cont.)

- (a) 4A Molecular sieve/sodium triacetoxy borohydride/dichloromethane/-20deg.
- (b) Tert.butylacetyl chlorid~~e~~/triethylamine/dichloromethane/R.T.
- (c) 3-Pyridylacetic acid/EDC/HOBT/N-methylmorpholine/dichloromethane/0deg-R.T.
- (d) Tributyltin hydride/bis(triphenylphosphine)palladium(0) chloride/dichloromethane
- (e) Trifluoroacetic acid/R.T.

- 166 -

Scheme 44



SUBSTITUTE SHEET (RULE 26)



- 167 -

## Scheme 44(cont.)

(a) 4A Molecular sieve/sodium triacetoxy borohydride/dichloromethane/-20deg.

(b) R=COCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>. Isovaleryl chloride/triethylamine/dichloromethane/R.T.

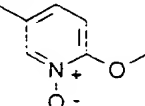
R=COCH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>. Tert. butylacetyl chloride/dichloromethane/triethylamine/R.T.

R=COCH<sub>2</sub> 3-Pyridylacetic acid/EDC/HOBT/N-methylmorpholine/dichloromethane.



R=COCH<sub>2</sub>

6-Methoxy-1-oxo-nicotinic acid/EDC/HOBT/N-methylmorpholine/  
dichloromethane.

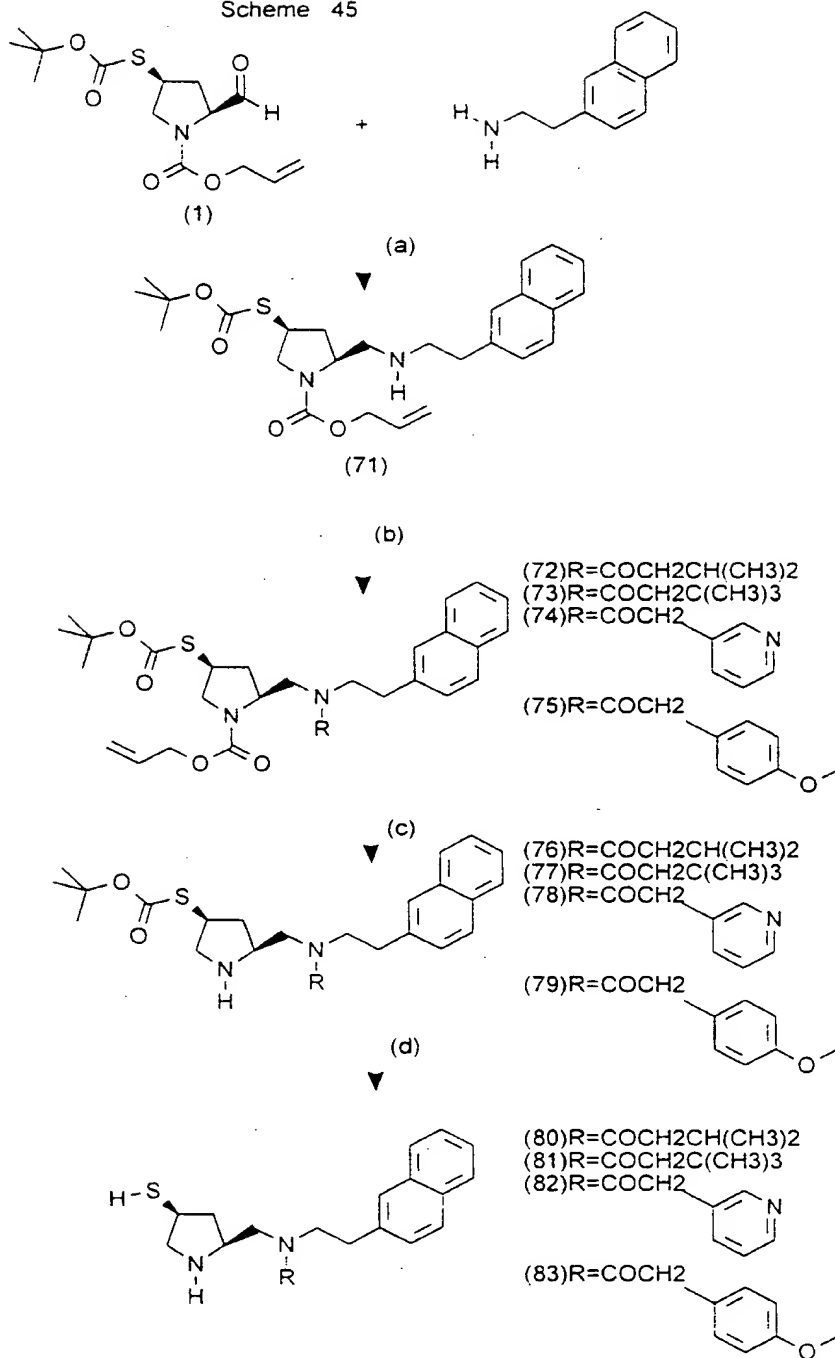


(c) Tributyltin hydride/bis(triphenylphosphine)palladium(0) chloride/dichloromethane

(d) Trifluoroacetic acid/R.T.

- 168 -

Scheme 45

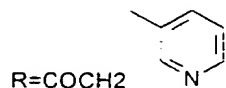
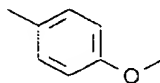


SUBSTITUTE SHEET (RULE 26)

- 169 -

## Scheme 45(cont.)

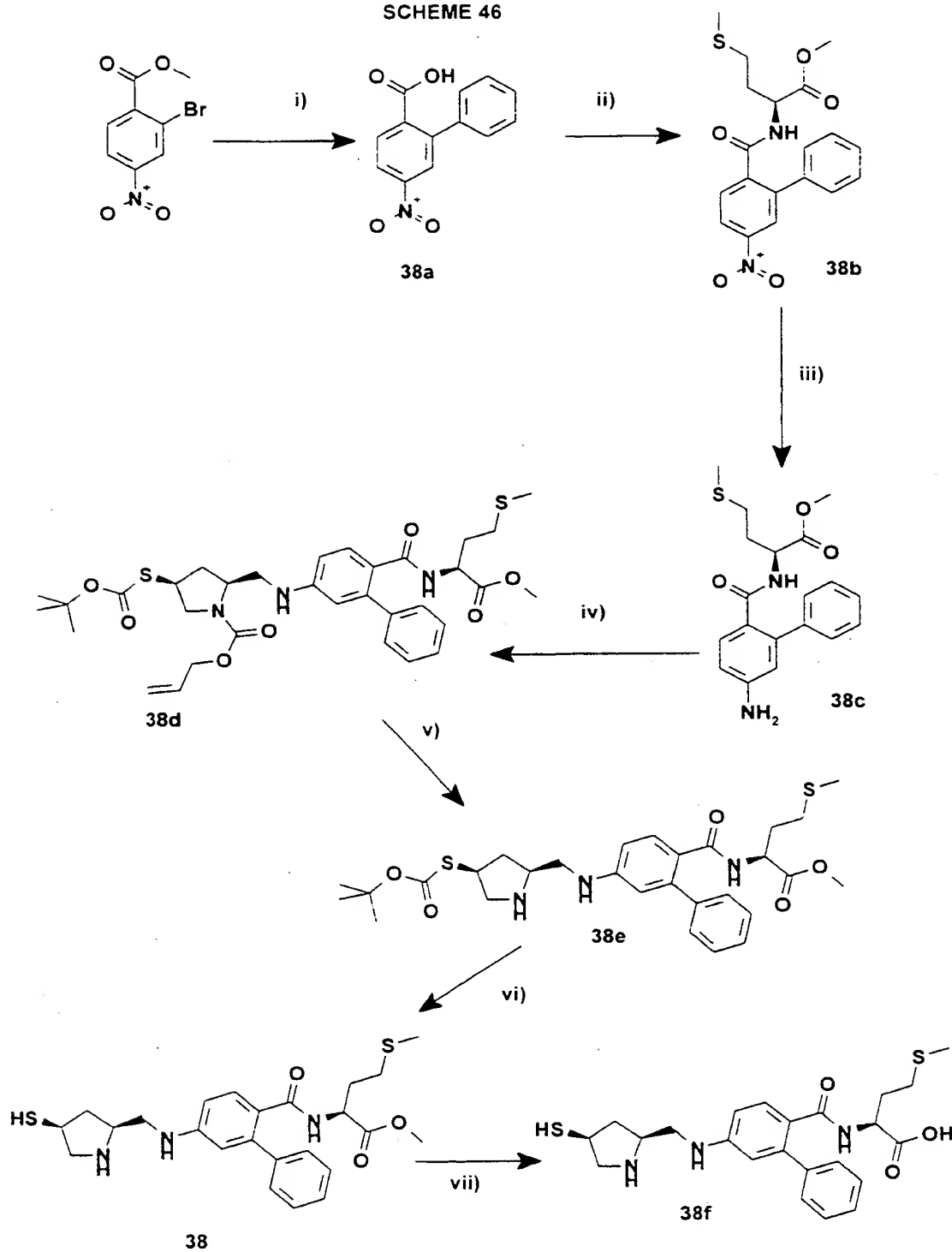
(a) 4A Molecular sieve/sodium triacetoxy borohydride/dichloromethane/-20deg.

(b) R=COCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>. Isovaleryl chloride/triethylamine/dichloromethane/R.T.R=COCH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>. Tert.butylacetyl chloride/dichloromethane/triethylamine/R.T.R=COCH<sub>2</sub> 3-Pyridylacetic acid/EDC/HOBT/N-methylmorpholine/dichloromethane.R=COCH<sub>2</sub> 4-Methoxyphenylacetic acid/EDC/HOBT/N-methylmorpholine/dichloromethane.

(c) Tributyltin hydride/bis(triphenylphosphine)palladium(0) chloride/dichloromethane

(d) Trifluoroacetic acid/R.T.

SCHEME 46



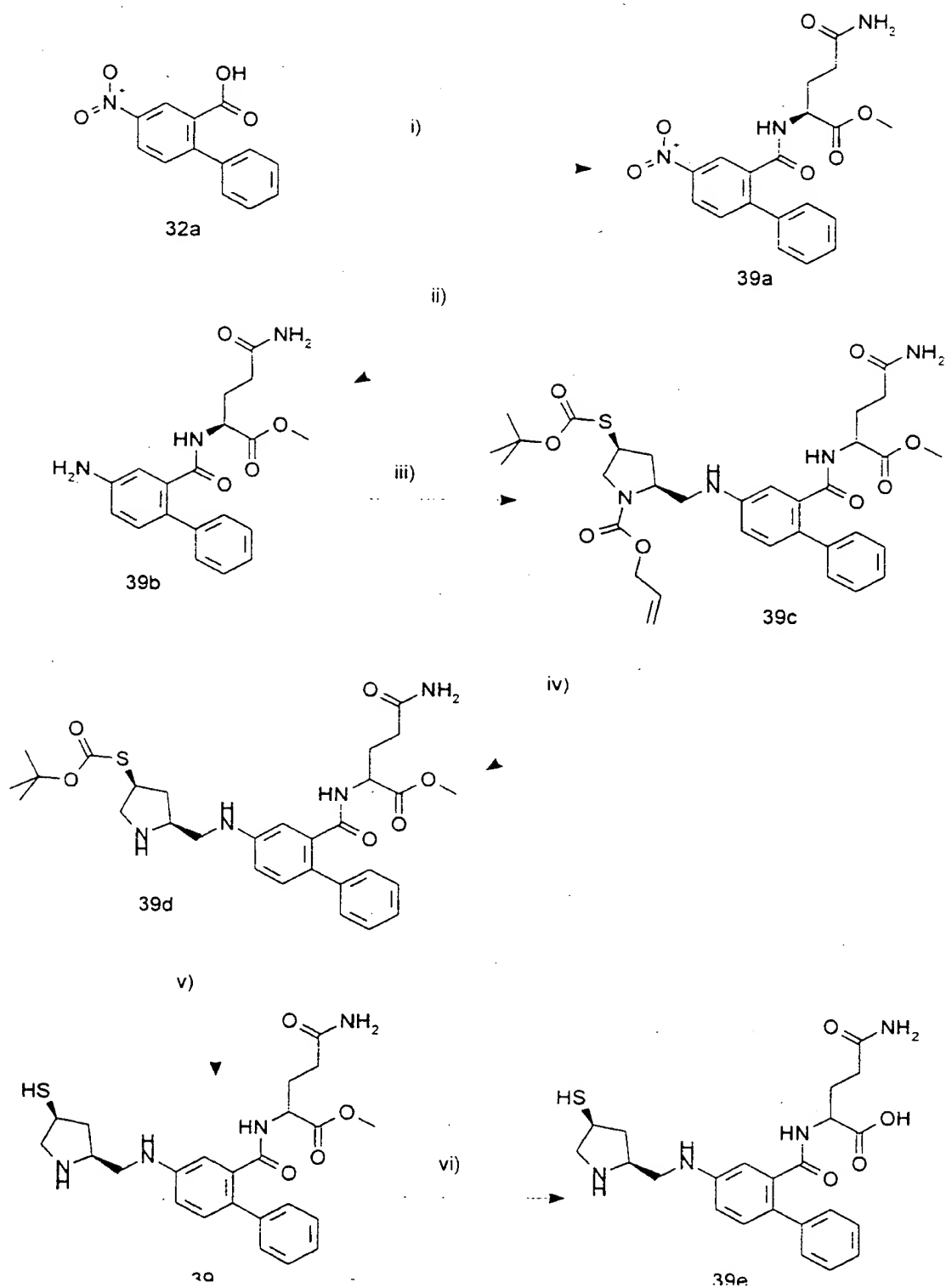
- 171 -

## SCHEME 46 (contd.)

- i)  $\text{PhB(OH)}_2$ ,  $(\text{PPh}_3)_4 \text{Pd}^0$  /DME. $\text{NaHCO}_3$ (aq)  $\Delta$  Reflux
- ii) EDC.HOBT/DMF  $0^\circ\text{C}$   
NMM.L-Methionine methyl ester hydrochloride  $0^\circ\text{C}$ -RT
- iii)  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ /EtOAc  $\Delta$  Reflux
- iv) **22b**/MeOH.  $3\text{\AA}$  sieves  
AcOH. $\text{NaCNBH}_3$
- v)  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $^n\text{Bu}_3\text{SnH}$ / $\text{CH}_2\text{Cl}_2$ . $\text{H}_2\text{O}$
- vi) TFA
- vii) 2N NaOH/MeOH

- 172 -

SCHEME 47



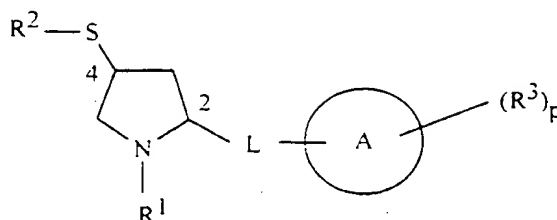
SUBSTITUTE SHEET (RULE 26)

- 173 -

- i) EDC.HOBT/DMF 0°C  
NMM.L-Glutamine methyl ester hydrochloride 0°C-RT
- ii)  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ /EtOAc  $\Delta$  Reflux
- iii) **22b**/MeOH.3A° sieves  
AcOH.NaCNBH<sub>3</sub>
- iv)  $\text{PdCl}_2(\text{PPh}_3)_2$ , <sup>n</sup>Bu<sub>3</sub>SnH/ $\text{CH}_2\text{Cl}_2$ , H<sub>2</sub>O
- v) TFA
- vi) 2N NaOH/MeOH

**CLAIMS**

1. A pharmaceutical composition comprising an inhibitor of ras farnesylation of Formula I



Formula I

wherein:

$R^1$  is selected from H;  $-C_{1-4}$ alkyl;  $-C_{1-3}$ alkylene-Ph optionally mono or di-substituted on Ph with substituents selected from  $C_{1-4}$ alkyl, halogen, OH,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkanoyl,  $C_{1-4}$ alkanoyloxy, amino,  $C_{1-4}$ alkylamino, di( $C_{1-4}$ alkyl)amino,  $C_{1-4}$ alkanoylamino, nitro, cyano, carboxy, carbamoyl,  $C_{1-4}$ alkoxycarbonyl, thiol,  $C_{1-4}$ alkylsulfanyl,  $C_{1-4}$ alkylsulfinyl,  $C_{1-4}$ alkylsulfonyl and sulfonamido;  $-CO-C_{1-4}$ alkyl;  $-CO-O-C_{1-4}$ alkyl;  $-CO-O-C_{2-4}$ alkenyl;  $-CO-O-(CH_2)_n$ Ph optionally substituted on Ph as defined for substitution on Ph in  $R^1 = -C_{1-3}$ alkylene-Ph in this claim 1 and  $n=0-4$ ;  $-C_{1-4}$ alkylene- $CONR^4R^5$  where  $R^4$  &  $R^5$  are independently selected from H,  $C_{1-4}$ alkyl; and  $-C_{1-4}$ alkylene- $COOR^6$  where  $R^6$  is selected from H,  $C_{1-4}$ alkyl;

$R^2$  is selected from H;  $-C_{1-4}$ alkyl;  $-C_{1-3}$ alkylene-Ph optionally substituted on Ph as defined for substitution on Ph in  $R^1 = -C_{1-3}$ alkylene-Ph in this claim 1;  $-COC_{1-4}$ alkyl; and  $-COOC_{1-4}$ alkyl;

20

$R^3$  is selected from H; OH; CN;  $CF_3$ ;  $NO_2$ ;  $-C_{1-4}$ alkyl;  $-C_{1-4}$ alkylene- $R^7$  where  $R^7$  is selected from phenyl, naphthyl, and a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and any aryl ring in  $R^7$  is optionally substituted as defined for substitution on the Ph group in  $R^1 = -C_{1-3}$ alkylene-Ph in claim 1;  $R^7$ :  $C_{2-4}$ alkenyl; halogen;  $-(CH_2)_nCOOR^8$  where  $n=0-3$  and  $R^8$  represents H.

25

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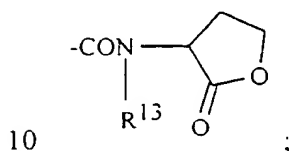
- 175 -

C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl; -CONR<sup>9</sup>R<sup>10</sup> where R<sup>9</sup> and R<sup>10</sup> independently represent H.

C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, -O-C<sub>1-4</sub>alkyl, -O-C<sub>2-4</sub>alkenyl, or -C<sub>1-3</sub>alkylenePh optionally substituted as defined for this group for R<sup>1</sup> in this claim 1; -CON(R<sup>11</sup>)OR<sup>12</sup> where R<sup>11</sup> and R<sup>12</sup> independently represent H, C<sub>1-4</sub>alkyl and C<sub>2-4</sub>alkenyl;

5 a group of Formula II, -CONR<sup>13</sup>-CHR<sup>14</sup>-COOR<sup>17</sup>, where R<sup>13</sup> is H or C<sub>1-4</sub>alkyl, R<sup>17</sup> is H or C<sub>1-6</sub>alkyl, R<sup>14</sup> is selected from the side chain of a lipophilic amino acid.

carbamoylC<sub>1-4</sub>alkyl, N-(monoC<sub>1-4</sub>alkyl)carbamoylC<sub>1-4</sub>alkyl and N-(diC<sub>1-4</sub>alkyl)carbamoylC<sub>1-4</sub>alkyl, the group of Formula II having L or D configuration at the chiral alpha carbon in the corresponding free amino acid; a lactone of formula



C<sub>1-4</sub>alkyl monosubstituted on carbon with =N-OH; a group of Formula -X-R<sup>15</sup> where X is selected from O, CO, CH<sub>2</sub>, S, SO, SO<sub>2</sub> and R<sup>15</sup> is selected from C<sub>1-6</sub>alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and any aryl ring in R<sup>15</sup> is optionally substituted as

15 defined for the Ph group in R<sup>1</sup> = -C<sub>1-3</sub>alkylene-Ph in this claim 1;

p is 0-3 in which R<sup>3</sup> values can be the same or different;

L is a linking moiety selected from the following groups written from left to right in

20 Formula I:

-CO-NR<sup>16</sup>- where R<sup>16</sup> is selected from H, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylene-Z, -CO-

C<sub>1-4</sub>alkylene-Z, -CO-C<sub>1-6</sub>alkyl, -COZ, and Z, and Z is selected from -O-C<sub>1-4</sub>alkyl, phenyl,

naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5

heteroatoms selected from O, N and S and any aryl ring in R<sup>16</sup> is optionally substituted as

25 defined for the Ph group in R<sup>1</sup> = -C<sub>1-3</sub>alkylene-Ph in this claim 1; -CH<sub>2</sub>-NR<sup>18</sup>- where R<sup>18</sup>

represents any value defined for R<sup>16</sup>; -CH<sub>2</sub>S-; -CH<sub>2</sub>O-; -CH<sub>2</sub>-CHR<sup>19</sup>- where R<sup>19</sup> represents

any value defined for R<sup>16</sup>; -CH=CR<sup>20</sup>- where R<sup>20</sup> represents any value defined for R<sup>16</sup>.

SUBSTITUTE SHEET (RULE 26)

- CH<sub>2</sub>NR<sup>21</sup>-T- where R<sup>21</sup> represents any value defined for R<sup>16</sup>. T represents -(CH<sub>2</sub>)<sub>n</sub>- where n is 1-4 and T is optionally monosubstituted with R<sup>22</sup> where R<sup>22</sup> represents any value for R<sup>16</sup> other than H; -CH<sub>2</sub>NR<sup>23</sup>-SO<sub>2</sub>- where R<sup>23</sup> represents any value defined for R<sup>16</sup>;
- CH<sub>2</sub>NR<sup>24</sup>-CO-T- where R<sup>24</sup> represents any value defined for R<sup>16</sup>. T represents -(CH<sub>2</sub>)<sub>n</sub>- where n is 0-4 and T is optionally monosubstituted with R<sup>29</sup> where R<sup>29</sup> represents any value for R<sup>16</sup> other than H; -CO-NR<sup>25</sup>-T- where R<sup>25</sup> represents any value defined for R<sup>16</sup>. T represents -(CH<sub>2</sub>)<sub>n</sub>- where n is 1-4 and T is optionally monosubstituted with R<sup>26</sup> where R<sup>26</sup> represents any value for R<sup>16</sup> other than H; -CH<sub>2</sub>S-T- where T represents -(CH<sub>2</sub>)<sub>n</sub>- where n is 1-4 and T is optionally monosubstituted with R<sup>27</sup> where R<sup>27</sup> represents any value for R<sup>16</sup> other than H; -CH<sub>2</sub>O-T- where T represents -(CH<sub>2</sub>)<sub>n</sub>- where n is 1-4 and T is optionally monosubstituted with R<sup>28</sup> where R<sup>28</sup> represents any value for R<sup>16</sup> other than H;

A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms where the heteroatoms are independently selected from

15 O, N & S;

or a -S-S- dimer thereof when R<sup>2</sup>=H; or a N-oxide thereof;

or an enantiomer, diastereoisomer, pharmaceutically acceptable salt, prodrug or solvate thereof together with a pharmaceutically acceptable diluent or carrier.

2. A pharmaceutical composition according to claim 1 in which R<sup>1</sup> is selected from H; -CO-O-(CH<sub>2</sub>)<sub>n</sub>Ph optionally substituted on Ph as defined for R<sup>1</sup> = -C<sub>1-3</sub>alkylene-Ph in claim 1 and n=0-4; -CO-O-C<sub>2-4</sub>alkenyl; -CO-C<sub>1-4</sub>alkyl; -C<sub>1-4</sub>alkylene-CONR<sup>4</sup>R<sup>5</sup> where R<sup>4</sup> & R<sup>5</sup> are independently selected from H, C<sub>1-4</sub>alkyl.
- 20

3. A pharmaceutical composition according to any one of claims 1-2 in which R<sup>2</sup> is selected from H and -CO-C<sub>1-4</sub>alkyl.

- 25 4. A pharmaceutical composition according to any one of claims 1-3 in which L is selected from -CH<sub>2</sub>-NR<sup>18</sup>-; -CH<sub>2</sub>NR<sup>21</sup>-T.

5. A pharmaceutical composition according to any one of claims 1-4 in which A is selected from phenyl, naphthyl, pyridyl and thienyl.

6. A pharmaceutical composition according to any one of claims 1-5 in which combinations of R<sup>3</sup> and p are selected from
- 30

SUBSTITUTE SHEET (RULE 26)

- 177 -

- i)  $R^3$  is selected from a group of Formula II;  $-C_{1-4}alkylR^7$ ;  $-O-R^7$  and;  $R^7$ ; and  $p=1-3$  with the proviso that one value of  $R^3$  is a group of Formula II;
- ii)  $p=0$  with the proviso that A is naphthyl and L is  $-CH_2NR^{21}-T$ ;
- iii)  $p=1$  with the proviso that  $R^3$  = a group of Formula II and A is naphthyl.

5 7. A pharmaceutical composition according to claim 1 in which

$R^1$  is selected from H;  $-C_{1-4}alkyl$ ,  $-C_{1-3}alkylene-Ph$  optionally mono or di-substituted on Ph with substituents selected from  $C_{1-4}alkyl$ , halogen, OH,  $C_{1-4}alkoxy$ ,  $C_{1-4}alkanoyl$ ,  $C_{1-4}alkanoyloxy$ , amino,  $C_{1-4}alkylamino$ ,  $di(C_{1-4}alkyl)amino$ ,  $C_{1-4}alkanoylamino$ , thiol,  $C_{1-4}alkylthio$ , nitro, cyano, carboxy, carbamoyl,  $C_{1-4}alkoxycarbonyl$ ,  $C_{1-4}alkylsulfinyl$ ,

10  $C_{1-4}alkylsulfonyl$ , sulfonamido;  $-CO-C_{1-4}alkyl$ ;  $-CO-O-C_{1-4}alkyl$ ;

$-CO-O-C_{2-4}alkenyl$ ;  $-CO-O-CH_2-Ph$  optionally mono- or di-substituted on phenyl with substituents selected from  $C_{1-4}alkyl$ , halogen, OH,  $C_{1-4}alkoxy$ ,  $C_{1-4}alkanoyl$ ,

$C_{1-4}alkanoyloxy$ , amino,  $C_{1-4}alkylamino$ ,  $di(C_{1-4}alkyl)amino$ ,  $C_{1-4}alkanoylamino$ , thiol,  $C_{1-4}alkylthio$ , nitro, cyano, carboxy, carbamoyl,  $C_{1-4}alkoxycarbonyl$ ,  $C_{1-4}alkylthiono$ ,

15  $C_{1-4}alkylsulfonyl$ , sulfonamido;  $-C_{1-4}alkylene-CONR^4R^5$  where  $R^4$  &  $R^5$  are

independently selected from H,  $C_{1-4}alkyl$ ;  $-C_{1-4}alkylene-COOR^6$  where  $R^6$  is selected from H,  $C_{1-4}alkyl$ ;

$R^2$  is selected from H;  $-C_{1-4}alkyl$ ;  $-C_{1-3}alkylene-Ph$ ;  $-COC_{1-4}alkyl$ ;  $-COOC_{1-4}alkyl$ ;

20

$R^3$  is selected from H; OH; CN;  $CF_3$ ;  $NO_2$ ;  $-C_{1-4}alkyl$ ,  $-C_{1-4}alkylene-R^7$  where  $R^7$  is selected from phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 3 heteroatoms selected from O, N and S;  $C_{2-4}alkenyl$ ; halogen;

$-(CH_2)_nCOOR^8$  where  $n=0-3$  and  $R^8$  represents H,  $C_{1-4}alkyl$ ,  $C_{2-4}alkenyl$ ;  $-CONR^9R^{10}$

25 where  $R^9$  and  $R^{10}$  independently represent H,  $C_{1-4}alkyl$ ,  $C_{2-4}alkenyl$ ,  $-O-C_{1-4}alkyl$ ,

$-O-C_{2-4}alkenyl$ ;  $-CON(R^{11})OR^{12}$  where  $R^{11}$  and  $R^{12}$  independently represent H,  $C_{1-4}alkyl$  and  $C_{2-4}alkenyl$ ;

a group of Formula II,  $-CONR^{13}-CHR^{14}-COOR^{17}$ , where  $R^{13}$  is H or  $C_{1-4}alkyl$ ,  $R^{17}$  is H or  $C_{1-6}alkyl$ ,  $R^{14}$  is the side chain of a lipophilic amino acid with L or D configuration at the

chiral alpha carbon in the corresponding free amino acid; C<sub>1-4</sub>alkyl monosubstituted on carbon with =N-OH; -SO-C<sub>1-4</sub>alkyl; -SO<sub>2</sub>-C<sub>1-4</sub>alkyl; a group of Formula -X-R<sup>15</sup> where X is selected from CO, CH<sub>2</sub>, S, SO, SO<sub>2</sub> and R<sup>15</sup> is selected from C<sub>1-6</sub>alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 3  
 5 heteroatoms selected from O, N and S;

p is 0-3 in which R<sup>3</sup> values can be the same or different;

L is a linking moiety selected from the following groups written from left to right in

10 Formula I:

- CO-NR<sup>16</sup>- where R<sup>16</sup> is selected from H, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylene-Z and Z is selected from -O-C<sub>1-4</sub>alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 3 heteroatoms selected from O, N and S; -CH<sub>2</sub>-NR<sup>18</sup>- where R<sup>18</sup> represents any value defined for R<sup>16</sup>; -CH<sub>2</sub>S-; -CH<sub>2</sub>O-; -CH<sub>2</sub>-CHR<sup>19</sup>- where R<sup>19</sup> represents  
 15 any value defined for R<sup>16</sup>; -CH=CR<sup>20</sup>- where R<sup>20</sup> represents any value defined for R<sup>16</sup>; -CH<sub>2</sub>NR<sup>21</sup>-T- where R<sup>21</sup> represents any value defined for R<sup>16</sup>, T represents -(CH<sub>2</sub>)<sub>n</sub>- where n is 1-4 and T is optionally monosubstituted with R<sup>22</sup> where R<sup>22</sup> represents any value for R<sup>16</sup> other than H, and provided at least one of R<sup>21</sup> and R<sup>22</sup> is H; -CH<sub>2</sub>NR<sup>23</sup>-SO<sub>2</sub>- where R<sup>23</sup> represents any value defined for R<sup>16</sup>; -CH<sub>2</sub>-NR<sup>24</sup>-CO-T- where R<sup>24</sup> represents any value  
 20 defined for R<sup>16</sup>, T represents -(CH<sub>2</sub>)<sub>n</sub>- where n is 0-4 and T is optionally monosubstituted with R<sup>29</sup> where R<sup>29</sup> represents any value for R<sup>16</sup> other than H, and provided at least one of R<sup>24</sup> and R<sup>29</sup> is H; -CO-NR<sup>25</sup>-T- where R<sup>25</sup> represents any value defined for R<sup>16</sup>, T represents -(CH<sub>2</sub>)<sub>n</sub>- where n is 1-4 and T is optionally monosubstituted with R<sup>26</sup> where R<sup>26</sup> represents any value for R<sup>16</sup> other than H, and provided at least one of R<sup>24</sup> and R<sup>25</sup> is H; -CH<sub>2</sub>S-T-  
 25 where T represents -(CH<sub>2</sub>)<sub>n</sub>- where n is 1-4 and T is optionally monosubstituted with R<sup>27</sup> where R<sup>27</sup> represents any value for R<sup>16</sup> other than H; -CH<sub>2</sub>O-T- where T represents -(CH<sub>2</sub>)<sub>n</sub>- where n is 1-4 and T is optionally monosubstituted with R<sup>28</sup> where R<sup>28</sup> represents any value for R<sup>16</sup> other than H;

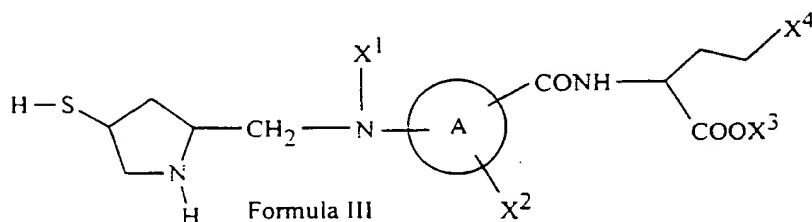
A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 3 or 5 heteroatoms in the case of monocyclic and bicyclic rings respectively where the heteroatoms are independently selected from O, N & S; or a -S-S- dimer thereof when  $R^2=H$ .

8. A pharmaceutical composition according to any one of claims 1-7 or claim 14 which is in the form of a tablet.

9. A compound as claimed in any one of compound claims 11-13 or a compound defined in any one of pharmaceutical composition claims 1-7 for use as a medicament.

10. A compound as claimed in any one of compound claims 11-13 or a compound defined in any one of pharmaceutical composition claims 1-7 for use in preparation of a medicament for treatment of a disease mediated through farnesylation of ras.

11. A compound of any of the following classes i). ii) or iii):  
class i)



15 wherein:

$X^1$  is selected from H;  $C_{1-6}$ alkyl; hydroxy $C_{1-6}$ alkyl;  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl;  $C_{1-6}$ alkylcarbonyl; hydroxy $C_{1-6}$ alkylcarbonyl;  $C_{1-6}$ alkoxy $C_{1-6}$ alkylcarbonyl;

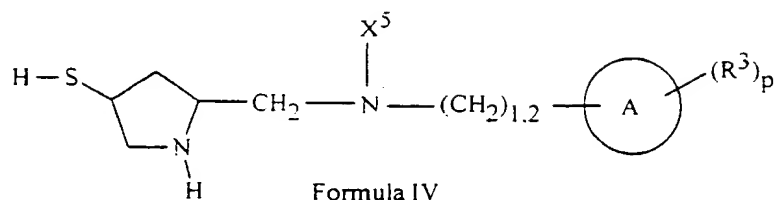
A is selected from phenyl, naphthyl or a 5-10 membered heterocyclic ring having upto 5 heteroatoms selected from O, N and S;

20  $X^2$  is selected from H; phenyl; phenyl $C_{1-6}$ alkyl; and a 5-6 membered heteroaryl ring containing upto 3 heteroatoms selected from O, N and S optionally linked to A by  $C_{1-6}$ alkyl; and  $X^2$  is optionally substituted on any ring, as defined for phenyl in  $R^1 = -C_{1-3}$ alkylene-Ph in claim 1;

$X^3$  is selected from H;  $C_{1-6}$ alkyl;

25  $X^4$  is selected from  $C_{1-6}$ alkylsulfanyl;  $C_{1-6}$ alkylsulfinyl;  $C_{1-6}$ alkylsulfonyl; carbamoyl;  $\underline{N}$ -( $C_{1-6}$ alkyl)carbamoyl;  $\underline{N}$ -(di $C_{1-6}$ alkyl)carbamoyl; and hydroxy or a  $C_{1-6}$ alkyl ether thereof;  
class ii)

- 180 -



wherein:

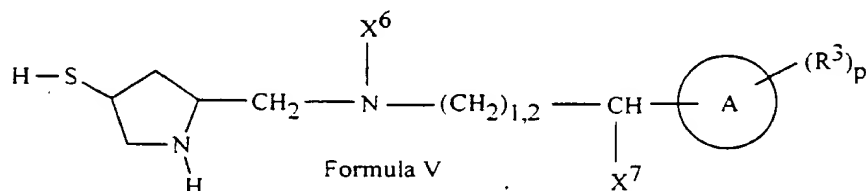
- $X^5$  is selected from  $-\text{CO}-\text{C}_{1-4}\text{alkyl}-\text{Ph}$ ;  $-\text{CO}-\text{C}_{1-6}\text{alkyl}$ ;  $-\text{CO}-\text{C}_{1-4}\text{alkyl}-\text{heteroaryl}$  where heteroaryl is a 5-10 membered heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and Ph or heteroaryl are optionally substituted as defined for Ph in  $R^1 = -\text{C}_{1-3}\text{alkylene}-\text{Ph}$  in claim 1;  $\text{C}_{1-4}\text{alkyloxyC}_{1-4}\text{alkyl}$ ;

A is naphthyl or a 10 membered heterocyclic ring having upto 5 heteroatoms selected from O, N and S;

$R^3$  and  $p$  are as defined in claim 1;

10

class iii)



wherein:

- $X^6$  has any value defined for  $X^5$  in ii) above;
- 15  $X^7$  is Ph optionally substituted as defined for Ph in  $R^1 = -\text{C}_{1-3}\text{alkylene}-\text{Ph}$  in claim 1;
- A is Ph or naphthyl or a 5-10 membered heterocyclic ring having upto 5 heteroatoms selected from O, N and S;
- $R^3$  and  $p$  are as defined in claim 1;
- or a N-oxide, pharmaceutically acceptable salt, prodrug or solvate thereof.

20

12. A compound according to claim 11 in which:  
in compounds of class i),

$X^1$  is selected from H and  $\text{C}_{1-6}\text{alkoxyC}_{1-6}\text{alkyl}$ ;

$X^2$  is selected from H; phenyl or  $\text{phenylC}_{1-6}\text{alkyl}$ ;

- 25  $X^4$  is  $\text{C}_{1-6}\text{alkylsulfanyl}$ ;

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A is selected from phenyl or naphthyl:

in compounds of class ii).

p is 0 and:

in compounds of class iii)

5  $X^7$  is Ph:

A is Ph:

p is 0.

13. Any one of the following compounds or a pharmaceutically acceptable salt thereof:

(2S)-2-{2-Benzyl-5-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-benzoylamino}-4-

10 methylsulfanylbutyric acid methyl ester :

(2S)-2-{2-Benzyl-5-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-benzoylamino}-4-

methylsulfanylbutyric acid :

(2S)-2-({2-phenyl-5-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester:

15 (2S)-2-({2-phenyl-5-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid:

(2S)-2-({3-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-naphthalene-1-carbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester ;

(2S)-2-({3-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-naphthalene-1-carbonyl)-

20 amino)-4-methylsulfanylbutyric acid :

(2S)-2-({3-phenyl-5[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid methyl ester;

(2S)-2-({3-phenyl-5[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-amino}-phenylcarbonyl)-amino)-4-methylsulfanylbutyric acid:

25 (2S,4S)-2-[{N-(4-methoxybenzyl)-N-(naphthalen-1-ylmethyl)-amino}-methyl]-pyrrolidine-4-thiol ;

N-(naphthalen-1-ylmethyl)-N-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-pentanamide :

N-(naphthalen-1-ylmethyl)-N-[(2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl]-2-(pyridin-3-yl)-acetamide ;

30 N-((2S,4S)-4-sulfanylpyrrolidin-2-ylmethyl)-3-methyl-N-(2-naphthalen-1-yl-ethyl)butyramide :

N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-N-(2-naphthalen-1-yl-ethyl)-2-pyridin-3-yl-acetamide :

(2S,4S)-2-{[(3-Methoxypropyl)-(2-naphthalen-1-ylethyl)amino]methyl}-pyrrolidine-4-thiol:

- 5 N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-2-(4-methoxy-phenyl)-N-(2-naphthalen-2-yl-ethyl)-acetamide ;

(2S,4S)-2-{[(2-(4-Methoxyphenyl)ethyl)-(2-naphthalen-1-ylethyl)amino] methyl}-pyrrolidine-4-thiol ;

N-(2,2-Diphenyl-ethyl)-N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-

- 10 butyramide ;

N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-2-yl-ethyl)-butyramide ;

N-(2,2-Diphenyl-ethyl)-N-([2S,4S]-4-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-butylamide ;

- 15 (2S)-2-{3-[(2S,4S)-4-Sulfanyl-pyrrolidin-2-ylmethyl)-(3-methoxy-propyl)-amino]-benzoylamino}-4-methylsulfanyl-butyric acid :

N-([2S,4S]-4-Sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-1-yl-ethyl)-butyramide ;

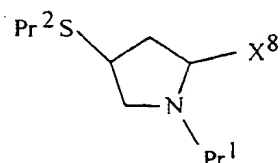
(2S)-4-Carbamoyl-2-({2-phenyl-5-[(2S,4S)-4-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-

- 20 phenylcarbonyl}-amino)-butyric acid; and

(2S)-4-Carbamoyl-2-({2-phenyl-5-[(2S,4S)-4-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-butyric acid methyl ester.

14. A pharmaceutical composition comprising a compound as defined in any one of  
25 claims 11-13 together with a pharmaceutically acceptable diluent or carrier.

15. A process for preparing compounds of classes i), ii) or iii) as defined in claim 11 which comprises deprotecting a compound of Formula VI



Formula VI



- 183 -

wherein  $X^8$  represents the right hand side of compound classes i), ii) or iii) as defined in claim 11,  $Pr^1$  is H or an amino protecting group,  $Pr^2$  is H or a thio protecting group and any functional groups in  $X^8$  are optionally protected with the proviso that there is at least one protecting group and optionally, if desired, converting the product thus obtained into a

5 pharmaceutically acceptable salt thereof.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 96/01810

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D207/12 C07D401/12 C07D409/12 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	EP 0 696 593 A (SQUIBB BRISTOL MYERS CO) 14 February 1996 cited in the application see the whole document	1-15
A	WO 94 04561 A (UNIV TEXAS ; GENENTECH INC (US); BROWN MICHAEL S (US); GOLDSTEIN JO) 3 March 1994 see page 37 - page 38	1-15
P,A	WO 96 09821 A (MERCK & CO INC ; ANTHONY NEVILLE J (US); DESOLMS S JANE (US); GRAHA) 4 April 1996 see page 39	1-15
	- / - -	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

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- \*G\* document member of the same patent family

Date of the actual completion of the international search

24 October 1996

Date of mailing of the international search report

31.10.96

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